Best of the 2005 AUA Annual Meeting

Highlights from the 2005 Annual Meeting of the American Urological Association, May 21-May 26, 2005, San Antonio, TX

[*Rev Urol.* 2005;7(3):145-182]

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Key words: α-Blockers • Benign prostatic hyperplasia • Bladder cancer • Botulinum toxin • Chronic prostatitis • Cryptorchidism • 5α-Reductase inhibitors • Kidney cancer • Lower urinary tract symptoms • Medical Therapy of Prostatic Symptoms (MTOPS) study • Minimally invasive therapies • Nomograms • Overactive bladder • Pediatric urology • Peyronie's disease • Premature ejaculation • Prostate cancer • Prostate Cancer Prevention Trial • Prostate-specific antigen • Prostate volume • Renal stones • Trospium chloride • Tyrol PSA Screening Project • Urothelial cancer • Vasectomy reversal • Vesicoureteral reflux

The Contributing and Medical Editors of *Reviews in Urology* were among the attendees at the 2005 American Urological Association (AUA) Annual Meeting in San Antonio. Here, they highlight the latest developments presented at this year's meeting in their respective areas of expertise.

Lower Urinary Tract Symptoms and Benign Prostatic Hyperplasia

Basic research and translational and clinical investigations into lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH) have been an important part of the AUA annual meetings over the last 10 to 15 years. In 2005, 116 presentations on LUTS and BPH were given as discussed or moderated posters and podium presentations, representing 6.7% of the total number of 1722 presentations. This percentage, which has varied slightly over the years, reflects the importance of this topic to both researchers and the practicing urologist attending the AUA meeting. The 116 presentations comprised 40 discussed posters in the Basic Research session, 20 moderated posters in the Epidemiology and Natural History/Evaluation of LUTS and BPH session, 12 podium presentations and 20 moderated posters on Surgical Therapy and New Technologies, and 24 podium presentations (divided into 2 sessions) on the very popular topic of Medical and Hormonal Therapy.

Basic Research

Dr. Bushman and his group from Madison, WI, have worked on sonic hedgehog signaling in the developing prostate for a number of years. It has been shown that sonic hedgehog expression in the epithelium of the developing urogenital sinus activates transcription factors in the adjacent mesenchyme, and that abrogation of

hedgehog signaling disrupts proper prostatic budding and branching. Until now, the target genes of hedgehog signaling in this context were not known. Lipinski and colleagues[1] demonstrated that insulin-like growth factor binding protein-6 (Igfbp-6) encodes a secreted peptide binding Igf-II and prevents its binding to the Igf-I receptor, which is important for the regulation of cellular proliferation, differentiation, and growth. In this work, it was demonstrated that sonic hedgehog signaling acts as an Igfbp-6, thus establishing for the first time a link between the hedgehog and Igf-II signaling pathways.

There is increasing evidence that estrogens might play an important role in the pathologic progress of BPH.

There is increasing evidence that estrogens might play an important role in the pathologic progress of BPH. Zhang and coworkers[2] studied the effects of 17-β estradiol on the expression of matrix metalloproteinase-2 and -9 (MMP-2, -9) and their tissue inhibitors in primary cultured prostate stromal cells. By demonstrating that estradiol effectively decreases the expression and secretion of MMP-2 and -9 exclusively through the estrogen receptor-α, they demonstrated that estrogens might have a modulatory effect on the developing prostatic matrix, suggesting that further investigation into the roles of estrogens in BPH is definitely warranted.

The Rho kinase (ROCK) molecule has been reported to play a role in the contraction of rat prostatic stromal cells. ROCK is involved in calcium sensitization, which has been reported to be as important as intracellular calcium concentration with regard to smooth muscle tone. Takahashi and associates[3] investigated the involvement of ROCK in the calcium sensitivity mechanism by studying it with the help of a ROCK inhibitor (fasudil). In an experimental setting, fasudil negates the calcium sensitization induced by ROCK. Noting the significant importance of calcium sensitization and intracellular calcium content with regard to smooth muscle contraction, the investigators speculate that this mechanism could represent a new therapeutic target to inhibit smooth muscle tone in BPH and thus ultimately affect LUTS and urodynamics.

Lucia and colleagues[4] performed an interesting quantitative morphometry analysis of the baseline biopsies of patients participating in the Medical Therapy of Prostatic Symptoms (MTOPS) study. Of the 3047 MTOPS patients, 1084 underwent a baseline biopsy from both peripheral and transition zones. The biopsy specimens of these patients were analyzed, and percent glandular epithelium and stroma/epithelium ratio were calculated. The findings were then correlated with progression events as defined by the MTOPS study. Lucia and colleagues demonstrated that percent epithelium was 9.1% lower in men experiencing a progression event, whereas the stroma/epithelium ratio was 17.7% higher in those experiencing a progression event. It therefore seems that the stromal component is of greatest significance in predicting whether or not patients will experience progression events as defined by MTOPS, namely, symptomatic progression, urinary retention, socially unacceptable incontinence, and other events. Further analysis of the MTOPS baseline biopsy data will likely be informative about other aspects of the natural history of the disease.

Collagen deposits in the detrusor of the obstructed bladder are an important part of the pathophysiologic findings associated with obstruction and secondary detrusor overactivity. Gomez and coworkers[5] demonstrated that increased collagen expression in the detrusor muscle of patients with BPH indeed correlates with decreased compliance of the bladder, increased detrusor activity, increased age, and increased rates of acute urinary retention (AUR). Levin and colleagues[6] demonstrated that experimental obstruction induces increased collagen synthesis within and between the bundles and cells of the detrusor smooth muscle. They further demonstrated that this increased density of collagen interferes with effective detrusor shortening during contraction. These investigators speculate that structural and functional alterations are responsible for the observed contractile dysfunction in this obstruction model.

Increased collagen expression in the detrusor muscle of patients with BPH correlates with decreased compliance of the bladder, increased detrusor activity, increased age, and increased rates of acute urinary retention.

An interesting observation was made by Lin and colleagues.[7] Cyclooxygenase-2 (COX-2) has been implicated in cellular growth regulation and progression of cancer. However, elevated COX-2 expression has also been described in BPH. It is also known that α-adrenergic stimulation

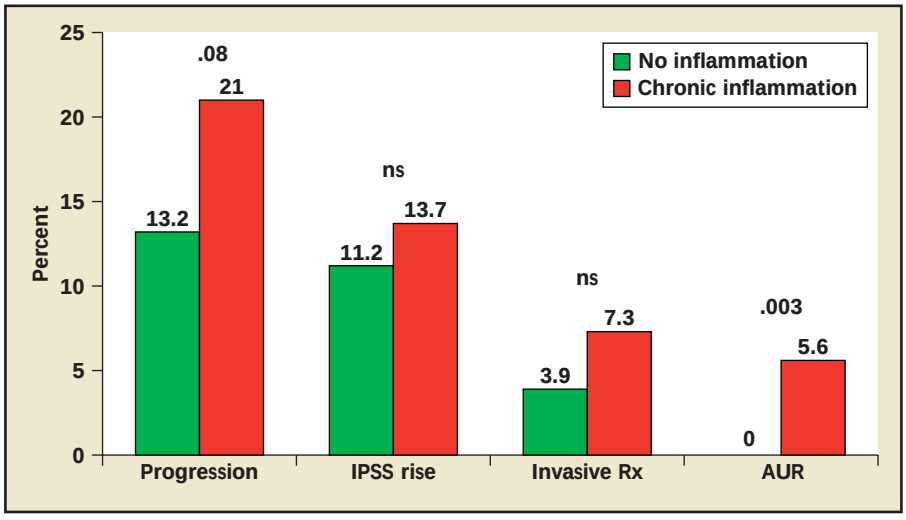
regulates cellular proliferation in a variety of tissues, including vascular smooth muscle, and that α-blockers might alter prostate stromal cell phenotype, whereas α stimulation might activate mitogen-activated protein kinase (MAPK) in prostatic cells. In a series of experiments, Lin and coworkers demonstrated that adrenergic stimulation with phenylephrine in human prostate stroma cells induces expression of COX-2, which is associated with cellular growth. They also found that MAPK signaling seems to play a key role in this induction, and they speculate that adrenergic stimulation might regulate cellular proliferation through MAPK activation and COX-2 upregulation. Given the recent interest in the expression and overexpression of COX-2 in both cancerous and benign proliferative tissues, these findings open a door to investigating the possibility of altering COX-2 upregulation as a therapeutic target in patients with LUTS and BPH.

Foster and colleagues[8] examined the effect of chronic treatment with the α-blocker doxazosin on gene expression of α-adrenoceptor subtypes in rat tissue. It has long been established that α-adrenoceptor antagonists, such as doxazosin, are effective in treating LUTS. However, molecular effects and differential gene expression associated with chronic doxazosin treatment have not been fully elucidated. These investigators demonstrated that doxazosin-treated rats had significantly heavier bladder base, prostatic urethra, and kidneys compared with age-matched controls. Polymerase chain reaction data showed that all 3 α1-adrenoceptor subtype messenger ribonucleic acids (mRNAs) are expressed in all tissues studied. Chronic doxazosin treatment caused an upregulation in mRNA levels of the predominant subtype in the tissue studied (ie, α1A in the rat bladder base, prostatic urethra, and kidney, α1B in the rat heart, and α1D in the rat aorta). In a subsequent study by these investigators,[9] gene expression profiling demonstrated that, under chronic doxazosin treatment, hundreds of genes were overexpressed, 43 of which were demonstrated to be related to cellular death, necrosis, or proliferation in G-protein signaling. Among the genes identified were the anti-apoptotic gene clusterin and the mitogen gene epiregulin. Gene expression profiling of this nature might provide further insight into the long-term effect and efficacy of α1-adrenergic receptor blockers in the treatment of LUTS and BPH.

Epidemiology and Natural History/Evaluation

It has long been known that men with BPH harbor chronic inflammatory infiltrates in 30% to 60% of cases, as evidenced by transurethral resection of the prostate (TURP) specimens. However, the importance of these chronic inflammatory infiltrates has never been fully elucidated. Roehrborn and colleagues[10] examined the baseline biopsy specimens from participants in the MTOPS study and showed that approximately 40% had chronic inflammatory infiltrates. Men with chronic inflammatory infiltrates in general were slightly older, had larger gland sizes (41 vs 37 mL), and higher serum prostate-specific antigen (PSA) levels (3.1 vs 2.3 ng/mL), whereas all other baseline parameters were identical. A very interesting observation was made regarding the fate of these patients in the placebo or nontreated group in MTOPS. Over an average follow-up period of 4.5 years, overall progression was noted in 13.2% of patients without inflammatory infiltrates but in 21% of patients with inflammatory infiltrates (P = .08). Similar increases in the rate of progression were noted for symptom progression and invasive therapy. Most notably, however, no patient without inflammation in the baseline biopsy experienced AUR, whereas among the patients with inflammatory infiltrates the AUR rate was 5.6% (Figure 1). These data suggest that the presence or absence of chronic inflammatory infiltrates in baseline biopsies has a profound impact on the natural history and progression of BPH and LUTS.

Figure 1. *Importance of inflammation in progression. Results from the Medical Therapy of Prostatic Symptoms study placebo group. IPSS, International Prostate Symptom Score; Rx, therapy; AUR, acute urinary retention; ns, not significant. Data from Roehrborn et al.*[10]



A strong relationship between severity of LUTS and sexual dysfunction has been demonstrated in a multitude of studies. In this session, 2 groups presented additional corroborative data. Crawford and coworkers[11] examined the Sexual Health Inventory for Men (SHIM) and correlated it with LUTS severity based on the categorization of mild, moderate, and severe symptoms in 6078 men participating in the Prostate Cancer Awareness Week. After controlling for age and other factors, the mean SHIM score was 17 for patients with mild, 14 for those with moderate, and 11 for patients with severe LUTS symptomatology, a lower SHIM score suggesting greater sexual dysfunction. Van Dijk and colleagues,[12] with a similar question in mind, presented a meta-analysis of 10 large-scale surveys involving more than 30,000 men. By multivariate analyses, they showed LUTS to be a risk factor for erectile dysfunction, ejaculatory dysfunction, and, in some trials, decreased libido. However, owing to the observational and mostly cross-sectional nature of these studies, causality cannot be implied.

Several investigators were interested in longitudinal changes in prostate volume, PSA level, and symptom severity, and the association between these changes. Ruud Bosch and Bohnen[13] analyzed changes in prostate volume and their ability to predict changes in symptom score over 4 years in the population-based Krimpen study. Of 864 men followed up for 2 years, 8.6% and 12% had true prostate volume increases defined as either an increase of 10 mL or 26%, respectively, from baseline. They observed that the chance of having a greater than 4-point increase in the International Prostate Symptom Score (IPSS) was significantly greater in the subset of men experiencing greater volume increases, and the chance for having an improvement by greater than 3 points was lower. This study suggests that longitudinal changes in prostate volume go hand in hand with longitudinal changes in symptom severity. A very similar study was presented on behalf of the Olmsted County Study of Urinary Symptoms in Men by St. Sauver and coworkers.[14] The Olmsted County study is now in its 10th year, and approximately 500 men underwent regular assessment according to IPSS, PSA level, flow rate, and transrectal ultrasound volume. For this particular analysis, the patients were divided by decade of life and then categorized as being either above or below the 80th percentile of PSA increase, above or below the 80th percentile of prostate volume increase, and above the 80th percentile on the slope of the IPSS increases. When analyzing the data by either univariate or multivariate analyses, it was shown that, for a patient above the 80th percentile of the PSA increase slope or the 80th percentile of the prostate volume increase slope, the respective odds ratios for being above the 80th percentile of the symptom score increase slope were 2.34 and 2.32 (univariate) and 1.84 and 1.91 (multivariate) (Table 1). The ability of PSA level and prostate volume changes over time to predict symptom worsening was similar to that of the baseline age of the patient, again suggesting how dynamic changes of volume and PSA are associated with dynamic changes of symptom severity. Last, de la Rosette and colleagues[15] examined the PSA velocity of 594 patients treated with watchful waiting or an α-blocker and followed up the patients longitudinally in their center. Although the overall PSA velocity was 0.01 ng/mL/y, these investigators found that a velocity of 0.5 ng/mL/y indicated increased risk for future invasive surgical therapy for BPH in these patients, again adding a dynamic component to the known predictive value of PSA for the natural history of BPH.

Regarding the static or baseline correlations between PSA and prostate volumes, 3 contributions were made. Slawin and coworkers[16] reported on

Table 1
Association Between Changes in IPSS, PSA Level, Volume, and Q_{max} in Olmsted County Study

	Odds Ratio	
Age (y)	Univariate Analysis	Multivariate Analysis
30-39	1.0	1.0
50-59	1.52	1.57
60-69	2.49	2.25
70+	3.02	2.63
PSA > 80th percentile	2.34	1.84
Q_{max} < 20th percentile	2.30	1.42
Volume > 80th percentile	2.32	1.91

Odds ratio for a patient to be above the 80th percentile on the International Prostate Symptom Score (IPSS) increase slope, depending on his age or being above the 80th percentile on the PSA rise slope or the volume increase slope, or below the 20th percentile on the Q_{max} slope. PSA, prostate-specific antigen; Q_{max}, peak urinary flow. Data from St. Sauver et al.[14]

PSA isoforms, namely BPH-related PSA (BPSA). They showed that whereas absolute free and total PSA levels are strongly correlated with parameters of prostate volume regardless of the likely presence of pathologic BPH, only BPSA levels correlated with the transition zone and total prostate volume, specifically, only in men likely to harbor pathologic BPH. Roehrborn and colleagues[17] again examined data from the MTOPS study, and in this case those patients were found to have stromoglandular hyperplasia on baseline biopsy. Surprisingly, not even half of all patients were found to have evidence of stromoglandular hyperplasia on baseline biopsy; undoubtedly, this is partially due to an undersampling of the entire prostate. The patients who did in fact have stromoglandular hyperplasia on baseline biopsy had a far better correlation coefficient between total prostate volume and serum PSA, of nearly 0.7, indicating an r^2 value of nearly 50%; this indicates that approximately 50% of the variability in prostate volume in these patients is explained by the total serum PSA value. This value is significantly higher than in unselected populations and suggests that in men with "true" BPH, the correlation between serum PSA level and prostate volume is quite strong. Cho and colleagues[18] from South Korea examined the relationship between PSA level and prostate volume in Korean men according to decade of life and found that this relationship is similar to that in Caucasians, although Korean men in general have lower PSA levels and smaller prostate volumes per decade of life. Nonetheless, as in Caucasians, PSA level might be used in Korean men to predict whether a given patient's prostate volume exceeds a certain threshold volume with reasonable clinical accuracy on the basis of receiver operating characteristic curve analysis.

Medical and Hormonal Therapy

One of the most important trials reported was a study randomizing 225 men over age 40 years with an AUA Symptom Inventory (AUASI) score between 8 and 35 points to either 160 mg of saw palmetto extract (*Serenoa repens*) b.i.d. or placebo over 1 year.[19] Patients in both groups experienced improvement over time; however, there were no differences in the magnitude of improvement between the 2 groups. The AUASI improvement was 2.3 in the saw palmetto group, versus 2.1 in the placebo group; the mean difference between the 2 groups was 0.23 mL/s for peak flow rate and 1.2 mL for prostate volume; none of these differences were statistically significant. This is one more trial casting doubt on the clinical efficacy of the currently used dosage of saw palmetto berry extract (160 mg b.i.d.) for men with LUTS and BPH. The National Center for Complementary and Alternative Medicine/National Institute of Diabetes and Digestive and Kidney Diseases–sponsored consortium charged to study phytotherapeutic agents in LUTS and BPH is currently preparing for a trial involving *Pygeum africanum* and saw palmetto compared with placebo later in the summer of 2005.

In a study of saw palmetto for BPH, the IPSS improvement was 2.3 in the saw palmetto group, versus 2.1 in the placebo group.

Several investigators studied the relationship between LUTS and sexual dysfunction, as well as the impact that certain α-blockers might have on sexual function or dysfunction. It has been stipulated that tamsulosin is unique among α-blockers, inasmuch as it induces ejaculatory dysfunction in a higher proportion of men compared with alfuzosin, doxazosin, or terazosin. In contrast, Barqawi and colleagues[20] examined data from 8076 men participating in the Prostate Cancer Awareness Week trial who answered both the AUASI and SHIM questionnaires. The mean results for the AUASI and SHIM, respectively, were 13 and 11.7 for men taking tamsulosin, 12 and 12.7 for those taking other BPH medication, and 6.9 and 15.6 for men taking no BPH medication. After adjusting for age and AUASI score, men taking tamsulosin had increases (ie, improvements) in the SHIM score, with increasing AUASI score suggesting for the first time a beneficial effect of tamsulosin. Others examined the role of alfuzosin and its impact on sexual function in open-label studies. Van Moorselaar and colleagues[21] examined the changes in sexual function, determined according to the main score on the Danish Prostate Symptom Score sexual-function questionnaire, in 3076 men taking part in a 12-month open-label study. They showed that sexual dysfunction was more severe in patients with more severe IPSS at baseline but that improvement from baseline was also greater. Similarly, Elhilali and coworkers[22] showed significant improvements in the 5 domains of the Brief Sexual Function Inventory in men treated with a real-life practice study over 2 years with alfuzosin 10 mg (Table 2).

In an extension of the Alfuzosin in Acute Urinary Retention study,[23] Roehrborn and colleagues[24] followed men who succeeded in a trial without catheter after receiving 2 to 3 days of alfuzosin 10 mg daily. Patients continuing after a successful trial without catheter after an episode of retention

Table 2
α-Blockers and Sexual Function

	Baseline	Change (%)	*P* value
IPSS	15.5	−7 (−38.5)	< .001
Nocturia	2.4	−0.9 (−30.4)	< .001
Bother score	3.8	−1.8 (−41.1)	< .001
BFSI domains			
Sexual drive	3.1	+0.1 (+5.7)	< .05
Erectile function	4.9	+0.2 (+12.9)	< .05
Ejaculation	4.2	+0.1 (+5.6)	.20
Problem assessment	4.2	+0.1 (+5.6)	< .05
Overall satisfaction	1.9	+0.2 (+18.4)	< .001

A total of 839 men with lower urinary tract symptoms and benign prostatic hyperplasia took part in a real-life practice study and were treated with alfuzosin 10 mg daily for 2 years. Significant improvements were noted at 2 years as measured by all instruments used, including the Brief Sexual Function Inventory (BFSI) and its 5 domains. IPSS, International Prostate Symptom Score. Reproduced with permission from Elhilali et al.[22]

do better if maintained on alfuzosin compared with placebo, with a significant reduction in the risk of secondary interventions or surgeries. Outcomes were predictable based on the amount of postvoid residual urine volume (PVR) and the serum PSA level, with those men with higher PVRs and higher serum PSA levels being less successful in avoiding surgery. This study suggests that a patient with urinary retention who has a successful trial without catheter after receiving an α-blocker might benefit in the long term from continuation of the α-blocker.

Two non–placebo-controlled comparison studies were presented that used different α-blockers. Koff and coworkers[25] reported on a trial involving 165 patients with BPH who were randomized to either doxazosin gastrointestinal therapeutic system 4 mg or tamsulosin 0.4 mg daily for 12 weeks. These investigators found nearly identical improvements in terms of symptom score, flow rate, and other parameters in the 2 groups, but earlier onset of improvement in the doxazosin than in the tamsulosin group, and at 12 weeks, an increased proportion of patients reporting ejaculatory difficulties in the tamsulosin group compared with the doxazosin group. This is not a surprising finding, given the higher probability of ejaculatory disturbances reported with tamsulosin compared with other α-blockers. Along this line, Wyllie and colleagues[26] sought to determine why all α-blockers are not equal with respect to sexual function and examined the pharmacologic and binding activities of quinazoline derivatives versus tamsulosin. They showed that all displayed a high affinity for the α1A, α1B, and α1D subtypes. However, whereas the quinazolines have more or less equal affinity for all 3 subtypes, tamsulosin has selectivity for α1A and α1D. A very important finding is that tamsulosin at concentrations that would be achieved at doses of either 0.4 mg or 0.8 mg daily demonstrates considerable interaction at serotonin and dopamine receptors. Taking these data together with other findings reported by Hellstrom and colleagues[27] at this year's AUA meeting, it is reasonable to assume that the selectivity for the serotonin and dopamine receptors exhibited by tamsulosin might be responsible for the increased incidence of ejaculatory disturbances. A group of Japanese investigators[28] randomized 144 patients to either an α1D-selective α-blocker (naftopidil) or tamsulosin. The interest in this trial stems from the observation and suggestion that the α1D receptor is overexpressed in the obstructed detrusor muscle, and thus that blocking the α1D receptor might be important in treating irritative symptoms, such as urgency, frequency, and nocturia. However, despite the theoretical consideration, patients in both groups experienced similar improvement not only in IPSS, quality-of-life score, urinary flow rate, and residual urine, but also in the irritative and obstructive subscores of the IPSS. It is therefore suggested that the selective inhibition of the α1D receptor does not confer superior benefits in terms of irritative symptoms (Figure 2).

Several abstracts were presented for studies of 5α-reductase inhibitors, and most of the data presented concerned the dual inhibitor dutasteride. Marks and colleagues[29,30] presented 2 abstracts from studies of the transition zone hypothesis. It has been suggested that 5α-reductase inhibitors have a stronger effect on the transition zone of BPH glands than on the peripheral zone, in line with the belief that the transition zone is the source and origin of BPH. By analyzing the data from the phase III dutasteride program, however, Marks and colleagues demonstrated that the volume shrinkage is exactly identical in the transition and peripheral zones and that the transition zone index (calculated as the ratio of transition zone

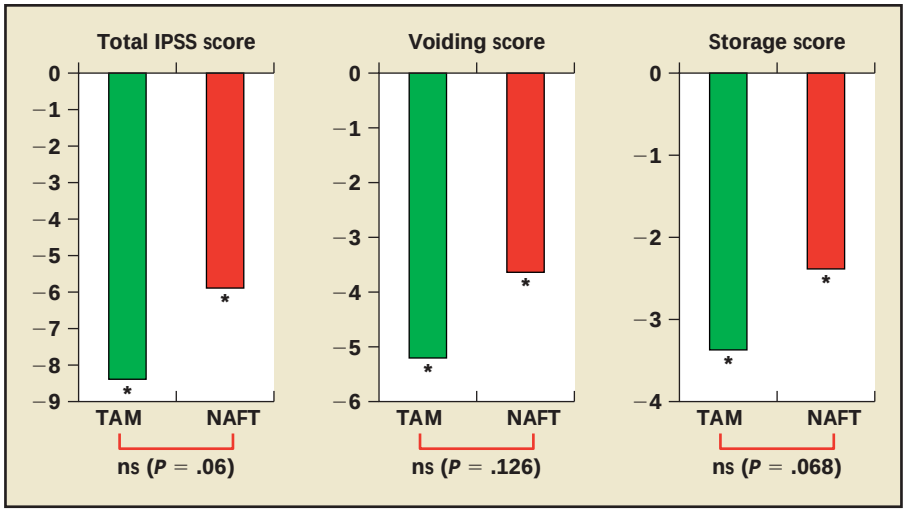


Figure 2. *Comparison of the α-blockers tamsulosin (TAM) and naftopidil (NAFT). *P < .01, Wilcoxon signed-rank test, Mann-Whitney U test. Data from Matsukawa et al.*[28]

volume to total prostate volume) remains at 0.5 from baseline to 24 months of follow-up and is identical for placebo and dutasteride. Thus, no differential effect was noted for 5α-reductase inhibitors on the different zones in the prostate. In the second part of this analysis, it was shown that the efficacy of dutasteride compared with placebo increases in men with larger prostates and with higher transition zone index tertiles. Both larger prostate volumes and higher transition zone indices are associated with a greater net improvement in terms of IPSS and a greater odds ratio for placebo- versus dutasteride-treated patients who experience either AUR or surgery (Table 3).

A new instrument was presented, namely, a BPH-specific lifestyle adaptation questionnaire.[31] Nineteen lifestyle adaptation mechanisms were queried, and in more than half of these adaptations, dutasteride-treated patients showed significant improvement in the adaptive mechanisms compared with the placebo group. Among these adaptive mechanisms were stopping frequently when driving, considering toilet facilities when planning daily activities, urinating before starting an activity, using a restroom whenever available, reducing the amount of fluid intake, and urinating before leaving home.

The question of whether the improvements obtained with 5α-reductase inhibitors are clinically significant has been raised in the past because the actual numeric improvements in symptom scores seem to be less with 5α-reductase inhibitors than with α-blockers. Roehrborn and Siami[32] addressed this issue by analyzing data from the dutasteride phase III trial program. By stratifying the patients by symptom severity at baseline into those with moderate versus severe symptoms, they showed an improvement in symptom score of 4.9 points in the moderately symptomatic group at baseline and 10.1 points in the severely symptomatic group at baseline, both results being highly significant statistically and clinically. These improvements are also significant based on the observations by Barry and colleagues published in *The Journal of Urology* in 1995,[33] which stipulated that a greater than 2-point improvement is needed in patients with baseline scores less than 20 points (ie, with moderate symptoms) and a greater than 6-point improvement in patients with baseline scores greater than 20 points (ie, in the severely symptomatic range) to

Table 3
Effect of Prostate Volume and Transition Zone Index on Dutasteride Treatment Outcomes

	IPSS			Odds Ratio		
TZI	PV ≤ 41 mL	PV 42–57 mL	PV ≥ 58 mL	PV ≤ 41 mL	PV 42–57 mL	PV ≥ 58 mL
≤ 0.39	0.9	1.3	3.2	1.24	0.99	0.76
0.4–0.54	1.8	2.8	2.4	1.55	1.78	3.93
≥ 0.55	3.5	3.2	3.3	6.17	2.16	3.29

Larger prostate volume (PV) *and* higher transition zone index (TZI) are associated with larger net improvements vs placebo in International Prostate Symptom Score (IPSS) and greater odds ratios for placebo vs dutasteride to experience acute urinary retention or surgery. Data from Marks et al.[29,30]

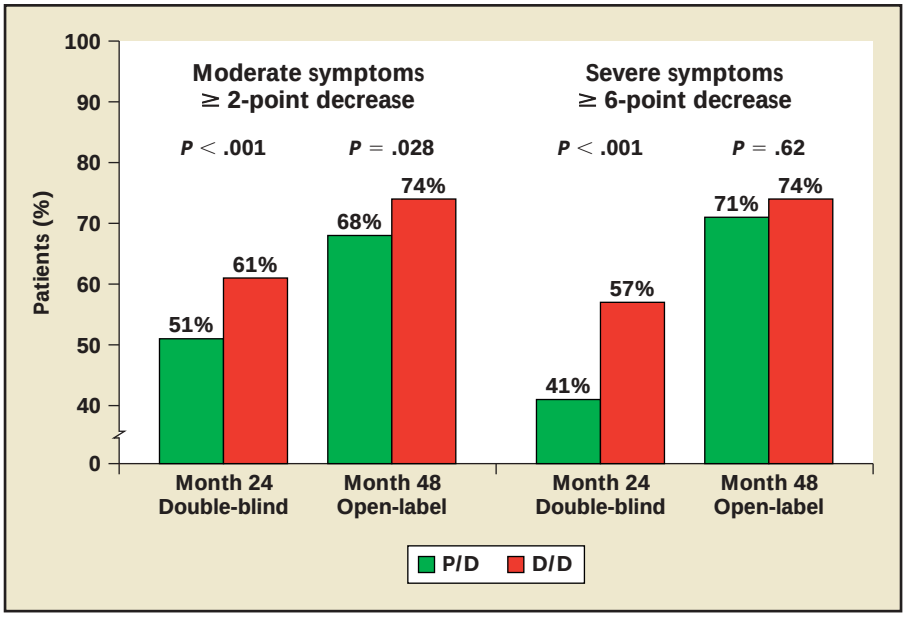


Figure 3. *Proportions of men classified as symptom responders at months 24 and 48 in a dutasteride phase III trial program, by baseline symptom severity (intention-to-treat population). P/D, placebo/drug; D/D, drug/drug. Data from Roehrborn and Siami.*[32]

achieve a clinically meaningful improvement. According to this classification, patients treated for 48 months with dutasteride had a probability of achieving a clinically significant improvement in 74% of cases, regardless of baseline symptom severity (Figure 3).

Several studies focused on further analyses of the MTOPS trial. The role of PVR was examined in detail by Roehrborn and colleagues.[34] PVR has been shown to correlate poorly with other baseline parameters, such as symptom severity, peak flow rate, and prostate volume, and it has not been found to be predictive of outcomes or symptom improvement. In the MTOPS study, baseline PVR was stratified into quartiles, and overall progressions were calculated for the 4 treatment groups. The highest PVR quartile in the placebo group had the highest rate and relative risk of clinical progression overall, and when the placebo group was analyzed for overall progression, symptom progression, and AUR, it seemed that both symptomatic progression and overall progression are significantly more likely in patients with higher baseline PVR values. In all 4 treatment groups there was a trend for the patients who experienced AUR to start out with higher baseline AUR values and to experience an ever-increasing amount of PVR until culminating in the AUR event. This suggests that AUR episodes in patients with LUTS and BPH are often preceded by an ever-increasing amount of PVR, ultimately leading to a decompensation of the bladder and the AUR event.

Another approach to analyzing predictors of outcomes, such as AUR or surgery, in the MTOPS study was undertaken by Slawin and coworkers.[35,36] They used a nomogram approach to predict symptomatic progression as well as AUR and surgery. Such nomograms allow one to take baseline characteristics, assign point values to these baseline characteristics, and calculate with reasonable clinical certainty whether symptom progression, AUR, or surgical events will occur in the subsequent 2 to 4 years. A somewhat surprising finding was made regarding the nomogram to predict AUR or surgery. Significant predictors of AUR or surgery were age, total PSA level, randomization to finasteride, and, surprisingly, the BPH Impact Index, a comparatively underused parameter. In contrast, peak urinary flow rate or IPSS were not predictive of episodes of AUR or surgery. In models that included prostate volume measurements PSA level did not prove to be predictive, presumably because of the high correlation between PSA level and prostate volume parameters. Nomograms of this nature are popular and often used in prostate cancer clinical prediction models. They might very well find a niche in predicting the progression and natural history of LUTS and BPH.

Patients treated for 48 months with dutasteride had a probability of achieving a clinically significant improvement in 74% of cases, regardless of baseline symptom severity.

Minimally Invasive Therapies and Surgical Interventions

Analyses from the National Institutes of Health (NIH)–funded Urologic Diseases in America Project, which abstracted data from Medicare and the nationally representative Health Care Utilization Project regarding the use of various surgical and minimally invasive treatments for BPH between 1992 and 1998, were presented by

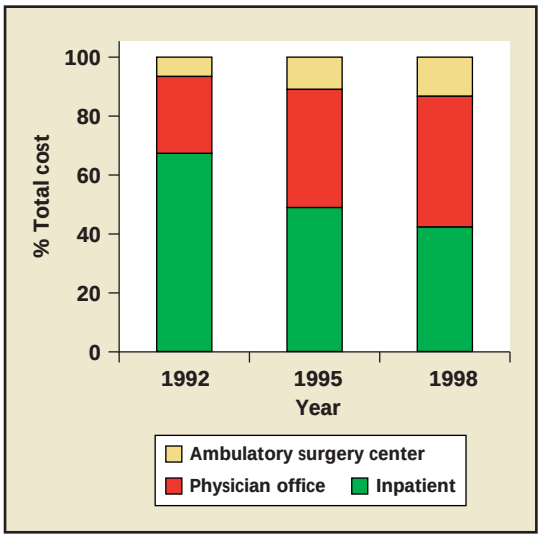


Figure 4. *Impact of contemporary management of benign prostatic hyperplasia on resource allocation and cost. A clinically significant trend toward greater use of minimally invasive surgical therapies, fewer admissions, and decreased length of stay shifted the cost from inpatient to outpatient sites and resulted in an overall direct cost savings for Medicare (58% decrease in inpatient cost, 19% increase in outpatient cost). Reproduced with permission from Kieran et al.*[37]

Kieran and colleagues.[37] These investigators demonstrated a clinically significant trend toward greater use of minimally invasive surgical interventions, fewer hospital admissions, and decreased length of stay, which eventually shifted the cost from inpatient to outpatient sites. This resulted in an overall direct cost savings for Medicare by decreasing inpatient cost by 58%, while increasing outpatient cost by only 19% (Figure 4).

Regarding the very controversial injection of botulinum toxin (BT) intraprostatically, 2 abstracts were presented.[38,39] The data could not be more conflicting. Larson and colleagues[38] initially presented data on a pilot group of 10 patients who were treated in a noncontrolled manner with 150 U of BT on either side of the prostate and showed significant improvement in their symptoms. The authors then reported on a randomized trial involving 30 patients with LUTS and BPH. These patients were randomized 2:1 to receive either 100 U of BT on each side or a similar volume injection of NaCl normal saline. When observed over time, both groups experienced identical improvements in symptoms, flow rate, and other parameters, suggesting no real benefit above and beyond a sham effect. In contrast, an Italian group[39] studied 16 patients treated with a total of 300 U of intraprostatic BT who were followed up for 6 months, but without a control group. The findings showed a significant improvement in symptom score, from 24 to 9 points, flow rate improvements from 8.2 to 18 mL/s, and, most remarkably, a decrease in prostate size from 106 to 53 mL. On the basis of these conflicting data, it is fair to say that, at this time, BT injection in the prostate for patients with LUTS and BPH cannot be endorsed as a validated and accepted treatment outside of research trials.

Regarding the very controversial injection of botulinum toxin intraprostatically, the data could not be more conflicting.

A new concept in the treatment of LUTS and BPH with minimally invasive therapies is photodynamic therapy with lemuteporfin, a benzoporphyrin derivative that serves as a chlorine-like photosensitizer, with a peak absorption in the region of red light at 689 nm. After injection of lemuteporfin, the prostate is treated with light; thus only the prostate parenchyma is effectively treated, and the urethral lining and the prostatic capsules are protected. Perez-Marrero and colleagues[40] presented the results from a multicenter dose-escalation study involving 29 patients, of whom 25 patients completed the trial. In general, the treatment was safe and well tolerated. Of 25 patients, 14 experienced a greater than 30% improvement in symptom score, and 8 of 25 experienced a greater than 50% improvement. A phase IIb dose-ranging study is ongoing.

In the area of microwave thermotherapy, several abstracts were presented regarding the most commonly used devices. Albala and colleagues[41] updated the data on the TherMatrx® TMx-2000 device (TherMatrx, Northbrook, IL). Of the original 200 patients treated with this device, 33 have now been followed up for up to 60 months, and the results in these patients were durable, with symptom score improvement from 21.4 to 12.4 and flow rate improvement from 8.6 to 13.6 mL/s. However, owing to the nature of the follow-up (mail-in questionnaires), retreatment rates in those patients who were not followed up are not known.

Data on a study of 120 patients with urinary retention randomized to either TURP or ProstaLund feedback thermotherapy (ProstaLund, Culver City, CA) were presented by Schelin and coworkers.[42] Ninety percent and 80%, respectively, of the patients treated became catheter free, and the improvements in symptoms and flow rate were similar. Thus, the ProstaLund

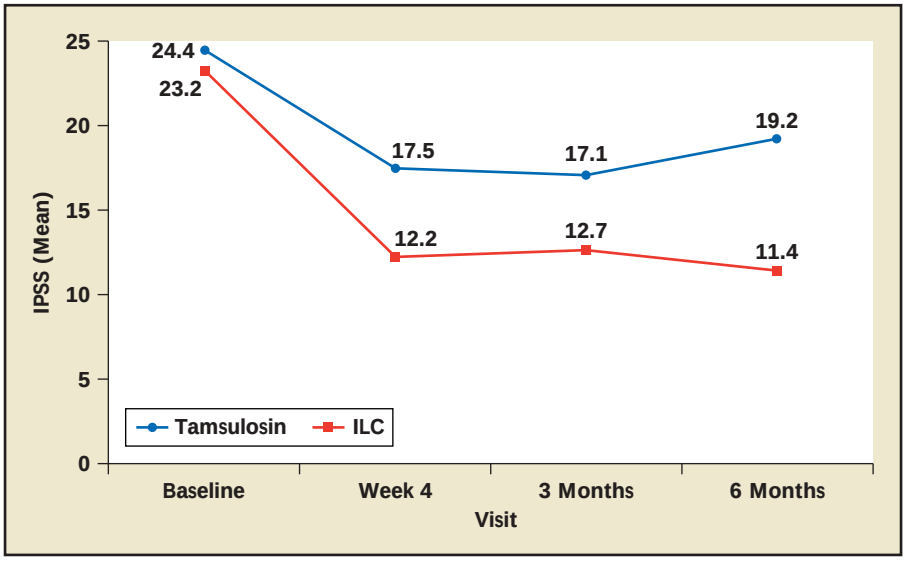


Figure 5. *Results from a randomized trial comparing tamsulosin with interstitial laser coagulation (ILC) with the Indigo® Optima laser. IPSS, International Prostate Symptom Score. Data from Roehrborn et al.*[44]

feedback thermometry unit might be suitable for patients presenting with AUR and not only for those with symptomatic BPH. Roehrborn and colleagues[43] updated the Urologix Cooled ThermoCath multicenter trial. At 24 months, the symptom improvement with the Cooled ThermoCath® (Urologix, Minneapolis, MN) treatment catheter included an improvement in symptom score from 20.8 to 9.9 points and an improvement in urinary flow rate from 8.3 to 11.8 points. Both absolute and percentage improvement with this 28.5-minute treatment are comparable to results with the older-style Targis treatment (Urologix), which was delivered over 60 minutes.

Two abstracts discussed treatment outcomes of interstitial laser coagulation (ILC) with the Indigo® Optima laser (Ethicon Endo-Surgery, Cincinnati, OH). The first study[44] featured an innovative design, namely a randomization between ILC Indigo Optima laser and tamsulosin (0.4 mg daily). This initial report on those patients who finished 6 months of follow-up demonstrated an improvement from 23.2 to 11.4 points in IPSS for the ILC group, compared with an improvement from 24.4 to 19.2 points in the tamsulosin group (Figure 5). Clearly, the data are not mature enough and the number of patients followed up not large enough to draw firm conclusions, but as this is only the second trial to randomize patients to either medical therapy or minimally invasive therapy, the data emerging should be watched with great interest. A Japanese group[45] identified factors associated with failure of ILC with the Indigo Optima laser device. They reported that patients with Schafer grade obstruction of greater than 3 had a significantly higher rate of failure, as did those with total prostate volumes of less than 41 mL. This suggests that the Indigo Optima laser technology is most suited for patients with moderate obstruction and true hyperplasia of the prostate (ie, an enlarged prostate gland).

Many abstracts focused on the potassium titanyl phosphate (KTP) or "GreenLight laser," also known as photoselective vaporization of the prostate (PVP), a technology produced by Laserscope (San Jose, CA). Because PVP with this device is similar to the ablation of prostate tissue with the old-style right-angle laser fibers, and because the learning curve is not as steep as for Holmium resection or enucleation of the prostate, PVP has found widespread acceptance both in the United States and abroad. Te and colleagues[46] reported on the initial 200 patients treated at New York Presbyterian Hospital. These patients had a mean prostate volume of 89 mL and were treated for an average of 96 minutes with IV sedation and spinal or general anesthesia. All but 5 patients were discharged within 23 hours. The symptom score at the time of latest follow-up had improved from 18.4 to 7.9, and the flow rate from 8.5 to 16.6 mL/s. Retreatment was comparatively rare, inasmuch as only 3 patients required retreatment at 12 months of follow-up. Bachmann and coworkers[47] reported on 42 patients in urinary retention compared with 56 patients who were not in retention and found similar postoperative catheterization times and similar outcomes in terms of symptom score and urinary flow rate. Postoperative retention requiring recatheterization occurred in 19% versus 11%, respectively, in the 2 groups. Equally good results with the PVP procedure were reported from Europe by Reich and colleagues[48] and Sulser and colleagues,[49] the latter comparing PVP and TURP in a randomized, controlled trial.

Matlaga and coworkers[50] reported on their experience with Holmium laser enucleation of the prostate (HoLEP) and specifically addressed the issue of the drop in serum PSA levels. In 116 patients, the PSA level fell from a preoperative mean of 7.32 ng/mL to a postoperative mean of 1.04 ng/mL, or 88.8%. This suggests a near total removal of all transition zone tissue, similar to that achieved by a very well

performed TURP or an open enucleation of the prostate. Peterson and colleagues[51] reported on 164 patients in urinary retention with a mean prostate weight of 107 g who underwent HoLEP. An average of 82 g was removed in an average of 98 minutes, with a mean catheterization time of 22 hours and a length of stay of 35 hours. The symptom score fell at 6 months to 4.0 points, with a mean peak flow rate of 24 mL/s.

Summary

The 2005 meeting of the AUA again provided a great number of presentations regarding LUTS and BPH. Although we still do not understand the ultimate cause of BPH, basic research findings advance our understanding of its etiology and perhaps point to new areas of therapeutic targeting. Natural history studies demonstrate that the interrelationship between prostate volume, PSA, and symptom severity is a dynamic one, inasmuch as changes in one parameter seem to be predictive of changes in another. Insights from medical therapy studies with α-blockers, 5α-reductase inhibitors, or combination therapy allow us to use different medications either alone or in combination in a more differentiated way, thus hopefully improving the efficacy of the treatment and, ultimately, the cost-effectiveness. In the area of minimally invasive treatments and surgical technologies, it seems that the KTP or GreenLight laser has gained considerable popularity owing to its ease of use and the rapid learning curve. The results are still considered short or intermediate term and therefore are not mature. Concern has been raised regarding the completeness of the tissue ablation in large glands and the potential for retreatment rates to be higher than after standard TURP. Resolution of this issue will come from appropriate long-term outcome studies. Regarding Holmium enucleation, it seems that long-term outcomes are excellent, and the significant drop in PSA level suggests that all available tissue from the transition zone is indeed effectively removed, thus in all likelihood predicting a very low rate of retreatment.
[Claus G. Roehrborn, MD, FACS]

Incontinence

Trospium Chloride Has Local Effect in the Bladder

Our group, from the University of Pittsburgh, presented new data at the AUA Annual Meeting from a recently completed research study in an animal model of the overactive bladder condition.[52] The data show that trospium chloride (Sanctura™; Indevus Pharmaceuticals, Inc., Lexington, MA) not only assists in controlling symptoms of overactive bladder when taken orally, but also controls symptoms when local contact is made with the bladder wall. Certain classes of drugs, when taken orally, can control the muscle contractions that cause conditions like overactive bladder. In this study, however, our group found that one drug, trospium chloride, reacts with the bladder muscle as urine is stored in the bladder. It is exciting to see that this drug could be helping patients with overactive bladder in more ways than was previously thought.

Study Design

Animals were given carbacol to induce bladder overactivity. The animals received, directly into the bladder, urine from human subjects taking either trospium, tolterodine LA, or oxybutynin XL, or urine from a control subject, in order to see whether any drug present in the urine following oral administration could reduce the effect of carbacol.

Study Findings

Urine from subjects who had taken trospium, when administered directly into the bladder of animals, blocked the effect of carbacol, demonstrating a local effect in the bladder. Conversely, carbacol-induced bladder overactivity was not blocked in animals whose bladders received urine from humans who had received tolterodine or oxybutynin or from the untreated control, demonstrating that there was no local effect from these agents.

These findings may be relevant given that 60% of the absorbed dose of trospium chloride is excreted into the bladder unchanged.
[Michael B. Chancellor, MD]

Renal Stones

The majority of renal stones are composed of calcium oxalate. Therefore, oxalate excretion plays a key role in stone formation in most patients. Approximately 50% of the urinary oxalate pool is derived from dietary sources. Oxalate is ubiquitous in plant-derived foods, making dietary control a difficult task. Oxalate decarboxylase is an enzyme that degrades oxalate into formate and carbon dioxide. The bacterium *Bacillus subtilis* produces this enzyme, but is unsuitable for human consumption. In contrast, *Lactococcus lactis* is a bacterium that can be safely consumed by humans, but does not produce the aforementioned enzyme. Chew and colleagues[53] tested whether the gene for oxalate decarboxylase (*yvrK*) could be cloned and expressed in *L. lactis*.

The coding region of *yvrK* from *B. subtilis* was amplified using polymerase chain reaction techniques. It was then cloned into the plasmid vector pMSP3535 downstream to the nisin promoter. When activated with nisin, this promoter induces *yvrK* expression. The vector was transfected into *L. lactis* and selected with erythromycin. The bacteria were then exposed to 1 mmol oxalate and varying

concentrations of nisin (0-50 ng/mL). It was demonstrated that oxalate degradation occurred only under nisin induction. Even at a low nisin concentration, 5 ng/mL, 90% of the oxalate was metabolized in 30 minutes. The authors hypothesize that the administration of this transformed bacterium could be used in the future as a probiotic therapy to reduce oxalate excretion. A number of steps need to be taken to reach this goal: 1) the bacterium's safety and effectiveness will have to be assessed in an animal model; 2) the ability of such a preparation to survive the acidic environment of the stomach will need to be determined; 3) the safety of administering genetically altered bacteria to humans will have to be established; 4) the efficacy in reducing oxalate excretion in humans will need to be demonstrated under controlled dietary conditions; and 5) the appropriate dosing regimen will have to be defined. Finally, it is anticipated that the bacterium would need to be administered with meals to allow for adequate oxalate degradation, especially since a significant amount of dietary oxalate may be absorbed in the small intestine.

[Dean G. Assimos, MD]

Prostatitis

Cutting-edge and state-of-the-art prostatitis research presented at the 2005 meeting of the AUA has expanded the clinical horizons of this enigmatic and difficult-to-manage syndrome.

Epidemiology

Epidemiological studies continue to improve our knowledge of the prevalence and characteristics of the prostatitis syndromes. A review of 225 patients in Korea diagnosed with acute prostatitis clearly showed that the most common causative organism remains *Escherichia coli* and that it is associated with significant prostate-specific antigen elevation.[54] Although acute prostatitis was treated with appropriate antimicrobial therapy, the progression to chronic prostatitis (CP) was observed in 5% to 8% of patients. This is one of the first studies to suggest that patients with acute bacterial prostatitis can progress to a CP syndrome.

The Boston Area Community Health (BACH) Survey of Urologic Symptoms determined an overall prevalence of prostatitis symptoms of 3.94% in a racially and ethnically diverse, randomly selected urban population.[55] This was one of the first studies to show that symptoms of prostatitis did not differ significantly by race/ethnicity or socioeconomic status but (as has been shown in previous studies) that they differed significantly by age group (higher prevalence with older age) and history of urinary tract infections.

Population-based epidemiological studies are the optimal approach to determine a true incidence of prostatitis. Clemens and colleagues[56] utilized coded physician diagnoses and subsequent chart reviews to estimate that the incidence of physician-diagnosed type 3 prostatitis was 3.0/1000/year. It is interesting that this value was essentially identical to the physician-diagnosed incidence rate of 3.1/1000/year reported in Olmsted County 7 years ago.[57] Prostatitis is a common condition in the community setting.

Prostatitis is associated with sexual and ejaculatory dysfunction (primarily pain) but not necessarily erectile dysfunction (ED). Zaslau and associates[58] administered the SHIM to 27 controls, 359 men presenting for evaluation of ED, and 108 men being treated for CP. Patients with CP had significantly lower total SHIM scores and SHIM question 1 scores (confidence to keep an erection) when compared with controls and patients seen for general urologic symptoms. It seems that CP may be an independent risk factor for ED.

Etiopathogenesis

New studies continue to question the role of microorganisms other than typical standard uropathogens in the etiology of chronic bacterial prostatitis. Riley and coworkers[59] showed inconsistent localization of gram-positive bacteria to prostate-specific specimens and an absence of bacteriuria caused by the same strains. It was suggested that gram-positive bacteria have only a limited etiological role in CP.

Another study, however, compared the clinical response and bacteriological eradication rates for traditional uropathogens and non-traditional uropathogens (primarily gram-positive organisms) in prostate-specific specimens in men diagnosed with chronic bacterial prostatitis treated with levofloxacin or ciprofloxacin.[60] These men had a mean duration of symptoms of 8.4 weeks (median of < 4 weeks) and were not heavily pretreated with antibiotics. It was demonstrated that bacterial eradication rates were similar in both groups (approximately 75%). The clinical success rates were also similar in both groups (around 75%), and in both groups there was a statistically significant correlation between clinical and microbiological outcomes. This interesting observation—that microbiological and clinical responses to fluoroquinolone therapy in chronic bacterial prostatitis were not dependent on whether traditional uropathogenic bacteria or non-traditional uropathogens were isolated—continues to fuel debate on the real role of gram-positive organisms in this disease.

Further complicating the discussion on the role of unusual organisms in CP, Shoskes and associates[61] showed that 60% of serum and 40% of urine

samples from 16 men with recalcitrant chronic pelvic pain syndrome (CPPS) refractory to multiple prior therapies had nanobacterial antigen or antibody. Therapy designed to eliminate nanobacteria resulted in significant improvement in the symptoms of recalcitrant CPPS in the majority of men. In 10 patients who had a post-therapy transrectal ultrasound, prostatic stones had decreased in size or were gone in 50% (nanobacteria are believed to be involved in the pathogenesis of kidney and perhaps prostatic calculi). This intriguing trial certainly suggests that a prospective placebo-controlled trial evaluating the role and therapy of nanobacteria in this disease is warranted.

Therapy designed to eliminate nanobacteria resulted in significant improvement in the symptoms of recalcitrant chronic pelvic pain syndrome (refractory to multiple prior therapies) in the majority of men.

Buyuktuncer and colleagues[62] evaluated the relationship of alanine or valine polymorphism at amino acid sequence 16 of manganese superoxide dismutase in CPPS patients compared with controls. In a small number of patients, they noted manganese superoxide dismutase polymorphism and suggested that this may be one of the mechanisms responsible for the etiology of category III CPPS. They also believe their data suggest that oxidative stress effects on CPPS should be further investigated.

Diagnosis

The 4-glass Meares-Stamey lower urinary tract evaluation test is not used by the majority of urologists (very few use it, in fact). The National Institutes of Health Chronic Prostatitis Collaborative Research Network evaluated 353 men who had non-missing values for baseline leukocyte counts and 2-day bacterial cultures on specimens obtained from a standard 4-glass test.[63] The researchers calculated that the implementation of a 2-glass pre- and post-massage test (PPMT) could reasonably and accurately predict white blood cell counts in expressed prostatic secretion (EPS). In 96% to 98% of the patients (depending on the diagnostic criteria), an accurate bacteriological diagnosis was made employing the PPMT. The PPMT has a strong concordance with the 4-glass test (good specificity), but the low sensitivity (50% chance of missing rare uropathogenic bacteria localized to EPS) needs to be considered in its clinical context. The PPMT seems to be a reasonable alternative, however, when EPS is not obtained.

Stern and coworkers[64] measured the inflammatory cytokines macrophage inflammatory protein-1α (MIP-1α) and monocyte chemoattractant protein-1 (MCP-1) in the EPS of healthy control men and men with CP/CPPS. They discovered that the chemotactic cytokines MIP-1α and MCP-1 are present and elevated in EPS from men with inflammatory CPPS and may play a role in the recruitment of inflammatory leukocytes in the inflamed prostate. MIP-1α and MCP-1 may prove to be biomarkers for CPPS. A diagnostic biomarker that allows accurate diagnosis of the condition and is responsive to improvement in symptoms would be a welcome addition to the urologist's armamentarium and would certainly stimulate more interest in research in the field.

Treatment

Two of the most common medications prescribed for CPPS include α-blockers and anti-inflammatories. Batstone and colleagues[65] reported a pilot study of 83 patients with CPPS randomized to placebo/placebo, tamsulosin/placebo, naproxen/placebo, and tamsulosin/naproxen. After 6 weeks of treatment, patients treated with tamsulosin and naproxen as single agents had modest benefit, whereas combination therapy was associated with a greater incidence of adverse events but did not provide any benefit over placebo.

Reissigl and associates[66] had previously reported on a randomized, placebo-controlled trial comparing a saw palmetto extract (*Serenoa repens;* Permixon; Pierre Fabre Medicaments, Castres, France) with placebo and determined that patients on active treatment were significantly better than placebo-treated patients at 6 and 12 months. At 12 months, the saw palmetto preparation was discontinued, and 2 years later there was follow-up on 55 of the original 72 patients initially treated with the saw palmetto. At 3 years, only 19% of patients could still be classified as responders. It appears that patients treated with saw palmetto-based phytotherapies must continue the medication long term if initial amelioration of symptoms is to be maintained.

Many urologists and researchers believe that the end stage in treatment-refractory CPPS patients is neurobehavioral. Anderson and associates[67] used myofascial muscular release therapy in conjunction with cognitive behavioral paradoxical relaxation therapy to address this component. More than half the patients treated this way had clinical improvement, but the optimistic statistical analysis provided by the authors and the lack of a sham therapy do not allow a definite conclusion as to the benefits of this therapy. The results are intriguing, however, and this type of neurobehavioral therapy should be

further investigated in a scientific prospective protocol.

Tripp and colleagues[68] examined a new model of depression in CP/CPPS utilizing a biopsychosocial framework (ie, physical, cognitive, environmental, and behavioral indices) in 150 men with CP/CPPS. The data strongly supported a biopsychosocial model in CP/CPPS-related depression and suggested that physicians may be able to advise patients to avoid certain pain-coping strategies associated with greater depression.

[J. Curtis Nickel, MD, FRCSC]

Prostate-Specific Antigen

A 2002 article by the Stanford group[69] created a firestorm with its implication that PSA had lost its discriminatory value in assigning risk assessment for prostate cancer. Stamey and colleagues stated that although PSA level correlated with tumor volume and other prognostic factors 20 years ago, in more recent times it has lost its predictive value. A number of presentations at the 2005 AUA meeting provided further information with respect to this controversy.

A 2002 article by the Stanford group created a firestorm with its implication that PSA had lost its discriminatory value in assigning risk assessment for prostate cancer.

Karakiewicz and associates[70] demonstrated the impact of PSA in men undergoing radical prostatectomy between 1996 and 2003. A total of 1448 men undergoing radical prostatectomy had their specimens evaluated under a stringent pathology protocol. The investigators used univariate linear progression models to assess the relationship between PSA and cancer volume and high-grade cancer volume. They divided their study into 4 equal quartiles according to the date of surgery. Contrasting the earliest and the latest time frame, the correlation (r^2) between PSA and prostate cancer volume decreased from 0.58 to 0.27 (Table 4). The investigators noted that this decrease was primarily related to the decrease in the volume of high-grade prostate cancer. A decrease in the correlation between PSA and high-grade prostate cancer was also observed, from 0.44 in the first quartile to 0.13 in the fourth. Karakiewicz and colleagues concluded that "a decrease in the rate of high-grade prostate cancer in radical prostatectomy specimens may be interpreted as a positive phenomenon, and is not synonymous with a loss of predictive significance from pretreatment PSA values." This report is important because it addresses a possible mechanism of the decreasing correlation between PSA and prostate volume: the reduction of high-grade disease, which might produce less PSA on a cell-by-cell basis, undoubtedly is

Table 4
Correlation Between PSA and Cancer Volume or High-Grade Cancer Volume for Each Quartile

	PSA vs Cancer Volume			PSA vs High-Grade Cancer Volume		
Quartile	All Patients (N = 1448)	PZ Patients (n = 1286)	TZ Patients (n = 155)	All Patients (N = 1439)	PZ Patients (n = 1277)	TZ patients (n = 155)
1 (n = 361) 01/08/1996–12/02/1998	0.58, 0.33	0.53, 0.28	0.78, 0.60	0.44, 0.19	0.44, 0.19	0.56, 0.32
2 (n = 364) 12/04/1998–05/08/2001	0.36, 0.13	0.38, 0.14	0.31, 0.10	0.24, 0.06	0.25, 0.06	0.70, 0.48
3 (n = 359) 05/09/2001–05/31/2002	0.49, 0.24	0.43, 0.19	0.61, 0.37	0.33, 0.11	0.36, 0.13	0.56, 0.32
4 (n = 364) 06/03/2002–10/10/2003	0.27, 0.07	0.22, 0.05	0.59, 0.35	0.13, 0.02	0.13, 0.02	0.18, 0.03

Values are correlation coefficient, r^2. TZ, transition zone cancer; PZ, peripheral zone cancer. Reproduced with permission from Karakiewicz et al.[70]

associated with increased volume of PSA-reducing cells and, perhaps more importantly, increased leakage between the cancer and, the systemic circulation.

A similar study presented by the Columbia group[71] asked the question, "Has pre-operative PSA lost the ability to predict biochemical failure after radical prostatectomy?" Mitchell and colleagues evaluated 1330 men undergoing radical prostatectomy between 1988 and 2003. Of these, 1246 men did not receive adjuvant therapy and constituted the study population. Patients were classified according to year of surgery. The investigators confirmed the effectiveness of PSA, Gleason score, and stage in predicting biochemical failure in univariate and multivariate models ($P < .001$). When they included the year of surgery in their model, they determined that the effect of PSA in predicting biochemical failure decreased over time ($P = .002$). However, when correcting for the effects of stage and grade, this deterioration in the ability of PSA to predict biochemical failure became insignificant. The major conclusion is that during the PSA era there has been a significant stage migration to more favorable tumors, and when this is considered in the analysis of PSA, the marker maintains its predictive ability.

Macejko and associates[72] sought to determine whether patients with PSA-detected cancer and large prostate volume have "clinically insignificant tumor." This would extend from the observation by the Stanford group[69] suggesting that the driver of elevated PSA in men is primarily benign prostatic hyperplasia. The investigators defined large prostate volume as a weight of 75 g or more, and they used Epstein's[73] and Ohori's[74] criteria to assess insignificant cancer. A total of 1258 men were evaluated; 1138 men had a prostate weight of less than 75 g, and 120 had prostates of 75 g or more. There was no statistically significant difference between the 2 cohorts according to either of the criteria for insignificant tumors (Table 5). There were more high-grade cancers in men with smaller glands; tumor volume less than 0.5 mL was found in none of the men with larger prostates but in 9% of those with glands less than 75 g. Five-year progression-free survival was no different between the 2 groups. The investigators concluded that most men with T1c prostate cancer and large prostate glands have clinically significant cancer.

Horninger and associates[75] evaluated the incidence of high-grade prostate cancer in 2074 screening volunteers (the Tyrol PSA screening study) undergoing biopsy who had PSA levels less than 4.0 ng/mL. Cancer was detected in 17.1%. The investigators demonstrated a stepwise increase in prostate cancer detection between group 1 (PSA level 1–1.99 ng/mL) and group 3 (PSA level 3–3.99 ng/mL), from 13.1% to 20.8% (Table 6). Moreover, contrasting these 2 groups, the percentage with high-grade cancer in the lower PSA cohort was 13%, compared with 21.7% in those with a PSA level in the upper range. This study mirrors quite well the observation from the Prostate Cancer Prevention Trial (PCPT) study[76] and provides a counter to the argument of lack of utility of PSA, because although both studies show a high yield of cancer in men with what was historically a "normal" PSA level, the yield within the low range correlates with PSA level.

Lucia and associates[77] from the PCPT reported on a study of PSA level as a predictor of adverse pathologic findings in radical prostatectomy

Table 5
Clinicopathology Features of Clinical Stage T1c Prostate Cancer and Progression-Free Survival (PFS) by Prostate Weight (PW)

	PW < 75 g (n = 1138)	PW ≥ 75 g (n = 120)	*P*
Age ≥ 60 y	808 (71)	102 (85)	.001*
Organ-confined	832 (73)	96 (80)	.112*
Gleason score 7–10	293 (27)	17 (14)	.003*
Preoperative serum PSA ≥10 ng/mL	83 (7)	20 (17)	< .001*
Percentage tumor < 5%	247 (29)	48 (59)	< .001*
Tumor volume < 0.5 mL	76 (9)	0 (0)	.005*
Positive surgical margins	248 (22)	23 (19)	.485*
5-Year PFS (95% CI)	89 (87-91)	91 (84-95)	.276†
10-Year PFS (95% CI)	79 (75-83)	85 (73-92)	
"Insignificant" tumors by Epstein criteria	3 (0.4)	0 (0)	.589*
"Unimportant" tumors by Ohori criteria	67 (8)	0 (0)	.008*

*χ^2 test.

†Wilcoxon test.

Data in parentheses are percentages unless indicated. CI, confidence interval; PSA, prostate-specific antigen. Reproduced with permission from Macejko et al.[72]

Table 6
Results from the Tyrol PSA Screening Study

	Tyrol Study		PCPT Placebo Arm	
	Prostate Cancer Detection Rate (%)	High-Grade Disease (Gleason Score ≥ 7) (%)	Prostate Cancer Detection Rate (%)	High-Grade Disease (Gleason Score ≥ 7) (%)
Group 1 (PSA 1–1.99 ng/mL)	13.1	13.0	17.0	11.8
Group 2 (PSA 2–2.99 ng/mL)	15.6	21.9	23.9	19.1
Group 3 (PSA 3–3.99 ng/mL)	20.8	21.7	26.9	25.0

PSA, prostate-specific antigen; PCPT, Prostate Cancer Prevention Trial. Reproduced with permission from Horninger et al.[75]

specimens. In the study, 278 prostatectomy specimens in the placebo group from the PCPT were evaluated. Adverse features included Gleason score of 7 to 10, pT3 disease, seminal vesicle invasion, and positive margins. One hundred and six men had high-grade prostate cancer. Forty-one men had stage pT3 disease. Table 7 shows the significant findings. These data are important because they derive from men subjected to biopsy as part of a study irrespective of clinical suspicion. They demonstrate that a PSA level in the low range provides stepwise risk stratification for adverse pathologic findings. This study, again in contrast to the initial report from Stamey and associates,[69] shows the persistent ability of PSA to predict adverse findings, although its major utility might be in the low PSA range.

In another study from the PCPT, Thompson and colleagues[78] studied 9459 men who were randomized to the placebo group of the PCPT trial. Of these, 5587 had at least one biopsy performed. The investigators performed area-under-the-curve (AUC) analysis of PSA results. Of the 5587 men, 21.9% were diagnosed with prostate cancer, including 250 with Gleason scores of 7 or greater (20.6% of the 1213 men with Gleason grade recorded). According to AUC analysis, the ability of PSA to predict prostate cancer or Gleason 7 prostate cancer versus no or low-grade prostate cancer was 0.682 and 0.782, respectively. The ability of PSA to predict prostate cancer with a Gleason score of 8 to 10 was significantly higher, with an AUC of 0.827. The investigators concluded that although the performance characteristics of PSA improved in predicting high-grade disease, the ability of PSA

Table 7
Pathologic Features at Prostatectomy and PSA

	PSA (ng/mL)				
	0–1	1.1–2.5	2.6–4.0	> 4.0	Total (n)
Gleason grade					
2–6	26	76	28	42	172
7–10	2	41	22	41	106
Total	28	117	50	83	278
P	.0002				
Stage					
pT2	26	101	41	60	228
pT3	0	13	8	20	41
Total	26	114	49	80	269
P	.0007				
Margin status					
Negative	26	94	35	60	215
Positive	0	20	14	20	54
Total	26	114	49	80	269
P	.008				

PSA, prostate-specific antigen. Reproduced with permission from Lucia et al.[77]

Table 8
PSA Results in Men with Prostate Volumes < 40 mL

Age (y)	Biopsy Result	n	Median PSA (ng/mL)	Interquartile PSA Range (ng/mL)	*P* (Positive vs Negative)
50–59	Positive	64	6.1	5.1–7.7	.001
	Negative	48	5.1	4.3–6.2	
60–69	Positive	81	5.7	4.9–6.8	.09
	Negative	54	5.2	4.7–6.3	
70–79	Positive	64	6.5	4.8–8.4	.06
	Negative	35	5.5	4.8–6.5	

PSA, prostate-specific antigen. Reproduced with permission from Presti et al.[79]

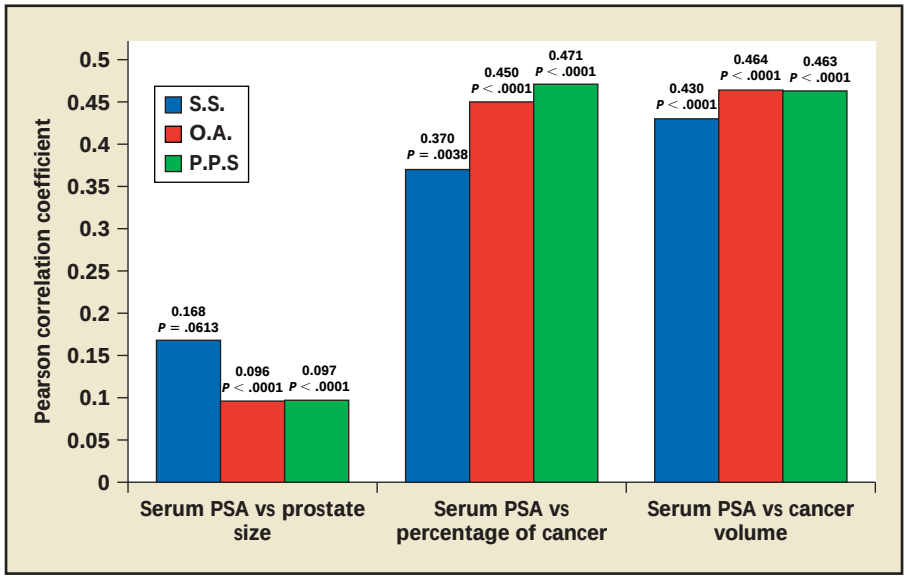
to detect all prostate cancer is lacking because of poor specificity at clinically meaningful levels of sensitivity.

Presti and associates[79] evaluated men with a PSA level between 4.0 and 10.0 ng/mL and prostate volumes less than 40 mL who underwent extended biopsy. The overall cancer detection rate was 41%. Median PSA levels were significantly higher in the positive-biopsy group in men who had prostate volumes less than 40 mL (6.1 vs 5.2 ng/mL) (Table 8). This report supports the earlier study from Stanford[69] suggesting that in glands with significant benign prostatic hyperplasia, the driver for PSA might not reflect the presence of cancer. However, in men with smaller glands, the ability to assign risk stratification according to PSA level remains.

Freedland and colleagues[80] also studied the relationship between prostate size and high-risk disease, along with biochemical progression after radical prostatectomy. A total of 791 men undergoing radical prostatectomy at several institutions were evaluated. According to multivariate analysis, there was a consistent pattern of inverse correlation between prostate size and adverse findings, including high-grade disease, positive surgical margins, and extracapsular extension (all $P < .01$). Moreover, smaller prostate weight was significantly associated with biochemical progression. The investigators concluded that prostate size might be a surrogate of androgen activity and suggest that their data are consistent with the hypothesis that tumors developing in states of lower androgen activity might be more aggressive.

Catalona and coworkers[81] provide perhaps the most significant data to counter Stamey and colleagues' 2002 report.[69] They investigated 3 cohorts of men undergoing radical prostatectomy: 2187 men from a screening study, 389 men treated by a single surgeon, and 401 men treated by a mixed group of private-practice clinicians. Tumor volume was estimated by multiplying the percentage of cancer reported by the pathologist by the prostate weight. In all 3 of the study cohorts, the correlation between PSA and percentage of cancer, as well as PSA and cancer volume, was greater than the correlation between PSA and prostate size (Figure 6). The investigators concluded that PSA continues to be a valid serum marker for prostate cancer. This certainly is a large study, derived from 3 separate cohorts of men. However, methodologic problems, primarily with respect to accuracy in estimating cancer volume, might in

Figure 6. *Serum prostate-specific antigen (PSA) level correlation to prostate size, percentage of cancer, and cancer volume. S.S., cohort of patients from a prostate cancer screening study (n = 2187); O.A., cohort of patients treated by one author (n = 389); P.P.S., cohort of patients treated by a mixed private physician staff (n = 401). Reproduced with permission from Catalona et al.*[81]



part explain the difference from the Stanford study.

Ultimately, additional studies will be required to delineate the role of PSA in cancer detection. But one is forced to agree with Dr. Stamey that we urgently require more specific markers in prostate cancer.
[Michael K. Brawer, MD]

Prostate Cancer

New Nomograms to Improve Prediction of Prostate Cancer Outcomes

The Merriam-Webster dictionary defines "nomogram" as "a graphic representation that consists of several lines marked off to scale and arranged in such a way that by using a straightedge to connect known values on 2 lines an unknown value can be read at the point of intersection with another line." The best example of and the most commonly used nomogram in prostate cancer is the one developed by Kattan and colleagues[82] to predict the risk of PSA progression following radical prostatectomy. Over time, however, the term "nomogram" has come to be used more loosely to also incorporate tables, such as the "Partin tables," which predict the risk of pathologic findings at the time of radical prostatectomy.[83]

Over the past several years, medicine in general, and specifically urology, has seen a growing number of nomograms. This year's meeting of the AUA was no exception.

Over the past several years, medicine in general, and specifically urology, has seen a growing number of nomograms. This year's meeting of the AUA was no exception. For example, 13 abstracts are listed in the program abstracts book under the keyword "nomogram," a total that does not include all the models that did not use the keyword "nomogram" in their titles. We have chosen to highlight a select few that make major contributions to our ability to prognosticate prostate cancer outcomes.

As stated above, the most commonly used nomogram today is the one described by Kattan and colleagues[82] to predict the risk of PSA progression after radical prostatectomy. Stephenson and colleagues[84] (including Kattan) presented a new and revised preoperative nomogram to predict the risk of PSA recurrence after radical prostatectomy. Two major differences distinguish the new nomogram from the original one: the new nomogram predicts the 10-year risk of recurrence as opposed to the 5-year outcomes in the original, and it includes the number of biopsy cores positive, which, as is becoming increasingly clear, is an important prognostic variable in prostate cancer. It should be noted that the predictive accuracy of the new model (0.77, on a scale where 1 is perfect and 0.5 is the flip of a coin) is similar to that of the original nomogram (0.76). However, the fact that the new nomogram predicts 10-year outcomes and that it is harder to predict long-term outcomes relative to short-term outcomes, makes the new model, which has a degree of accuracy similar to that of the original, a major step forward.

As we have learned since the publication of the original Kattan nomogram in 1998, not all men with a PSA recurrence will have a rapid clinical course. Therefore, importantly, Dotan and coworkers[85] and Freedland and associates[86] are developing new nomograms that predict the risk of metastasis and the risk of prostate cancer death, respectively, among men who have had a PSA recurrence. Before describing these 2 nomograms in detail, one important distinction is required. The preoperative nomogram described by Stephenson and colleagues[84] applies to the risk of PSA recurrence among *all* men undergoing radical prostatectomy. The nomograms by the Dotan and Freedland groups predicting progression and death, respectively, after biochemical recurrence apply *only* to men who have already developed a biochemical recurrence.

Dotan and colleagues[85] developed a nomogram that predicts the likelihood of developing metastatic disease within 8 years after biochemical recurrence. The variables included in the nomogram were presence of seminal vesicle invasion, high-grade pathologic disease, PSA doubling time at the time of recurrence, and PSA value at the time of recurrence. The model very accurately predicted the risk of developing metastasis, with an accuracy of 0.89.

Freedland and associates[86] developed a model to predict risk of prostate cancer death following biochemical failure. The model was then used to develop tables to predict the likelihood of prostate cancer survival at 5, 10, and 15 years after biochemical failure. The variables in the model included high-grade pathologic disease, time from surgery to biochemical recurrence, and PSA doubling time at the time of recurrence—variables similar to those used in the Dotan study. Importantly, patients could be risk stratified into groups with prostate cancer survival ranging from 94% to $< 1\%$ at 15 years after biochemical recurrence. The tables were developed in a style similar to the Partin tables and should greatly facilitate decision making about how

best to treat men with biochemically recurrent disease after radical prostatectomy.

Haese and coworkers[87] in 1 study developed 4 nomograms to predict the likelihood of insignificant cancer and various cancer volumes (ie, > 0.5 mL, > 1 mL, and > 2 mL) at the time of radical prostatectomy. The impetus for this study was the growing awareness that many men are overtreated for their cancers. One method of predicting clinically indolent cancer is by looking at clinically "insignificant cancers," defined as having a tumor volume < 0.5 mL and no Gleason pattern 4/5. Variables included in the models were PSA, biopsy Gleason sum, cumulative length of all cancer tissue (in mm), and percentage of biopsy cores with cancer. Overall, the nomograms worked very well, with predictive accuracies ranging from 0.82 to 0.87.

Collectively, these nomograms and tables will add to our ability to predict important events in prostate cancer, starting from the likelihood of insignificant cancer at the time of surgery to risk of recurrence after surgery, and even to predict longer-term events such as metastasis and prostate cancer death. Clearly, nomograms have aided our ability to predict outcomes for our patients and will continue to do so for the foreseeable future.

[Stephen J. Freedland, MD, Alan W. Partin, MD, PhD]

Male Sexual Health

A great deal of interest has been focused on the area of male sexual health during the past decade. The primary area of interest has been erectile dysfunction, and a number of important treatment options have become available for this condition over the past several years. Although the use of phosphodiesterase-5 (PDE-5) inhibitors has revolutionized the management of erectile dysfunction, substantially less attention has been paid to another important concern in male sexual health—premature ejaculation. Although the selective serotonin reuptake inhibitors (SSRIs) have been used in an off-label fashion for the management of premature ejaculation, a number of obstacles exist for the use of such agents to treat this condition. The relatively long half-life of the SSRIs limits their utility in the management of premature ejaculation since they do not yield optimum results when used on an as-needed basis. Moreover, the side effect profile for the SSRIs may pose a problem in some patients. Finally, limited data exist regarding the application of this class of agents to the treatment of premature ejaculation.

Several informative presentations were made at this year's meeting of the AUA regarding the management of premature ejaculation. Pryor and colleagues[88] evaluated the use of a new agent, dapoxetine, in the management of premature ejaculation. In this study, 2614 men were enrolled in 2 randomized, double-blind, placebo-controlled, multi-center clinical trials. Each patient received 12 weeks of treatment consisting of either placebo, 30 mg of dapoxetine, or 60 mg of dapoxetine. The medication was taken 1 to 3 hours before anticipated intercourse. Patients treated with dapoxetine were noted to have a significant improvement in their intravaginal ejaculatory latency time and experienced an improved sense of control over ejaculation as well as increased satisfaction with sexual intercourse. The results of this study suggest that dapoxetine is a promising method of therapy for the management of premature ejaculation.

Another presentation reported on the use of vardenafil versus sertraline in the management of premature ejaculation.[89] In this cross-over designed study, Sommer and associates concluded that vardenafil yielded substantial improvement in intravaginal ejaculatory latency time. Partners' sexual satisfaction also improved. The results using vardenafil seemed to be superior to those achieved using sertraline.

An area of male sexual health that is receiving substantial attention at this time is the potential for restoring sexual function for patients who have undergone radical retropubic prostatectomy for the treatment of prostate cancer. It has been postulated that early intervention with a variety of restorative treatments for erectile dysfunction may improve the outcome of sexual function following radical prostatectomy. Raina and coworkers[90] described initiation of therapy utilizing intraurethral MUSE® (alprostadil; VIVUS, Inc., Mountain View, CA) suppositories among 91 patients who had undergone radical prostatectomy. Patients receiving MUSE were given 125 μg of the agent 3 times per week for the first 6 weeks followed by 250 μg 3 times per week for 4 months. Patients who could not tolerate 250 μg remained at a dose of 125 μg. Patients receiving active treatments were compared with those receiving placebo. At the end of 6 months, 58% of patients in the MUSE group had natural erections sufficient for vaginal penetration without MUSE. In the control group,

The relatively long half-life of the SSRIs limits their utility in the management of premature ejaculation since they do not yield optimum results when used on an as-needed basis.

30.7% of patients achieved natural erections sufficient for vaginal penetration. The authors concluded that early MUSE therapy following radical prostatectomy increases the frequency of sexual activity and increases the likelihood of erections sufficient for intercourse.

In the area of male reproductive medicine and surgery, one of the most commonly performed procedures is vasectomy reversal. Although performance of a vasovasostomy is a relatively straightforward microsurgical procedure, performance of vasoepididymostomy is a more demanding and complex operation. For this reason, the more accurately the potential need for vasoepididymostomy can be predicted preoperatively, the better a urologic surgeon will be able to counsel his or her patients. Taylor and Fuchs[91] reported the results of a retrospective assessment of 2444 men who underwent vasectomy reversal performed by the senior author (Dr. Fuchs). Using widely recognized criteria for performance of vasoepididymostomy, the authors stratified their patient population based on elapsed time since performance of vasectomy and assessed the percentage of patients requiring vasoepididymostomy. As might be expected, patients who were 0 to 3 years from vasectomy required vasoepididymostomy infrequently (3% of procedures). Patients who were 10 to 11 years post-vasectomy required vasoepididymostomy in 36% of cases, and patients who were greater than 20 years from vasectomy required either unilateral or bilateral vasoepididymostomy in 67% of cases. Based on these findings, the authors concluded that the period of time that has elapsed since the performance of vasectomy is a major determinant of the potential need for a vasoepididymostomy. Such information should prove useful to urologic surgeons discussing the prognosis for vasectomy reversal with their patients.

The criteria for performance of vasoepididymostomy rather than vasovasostomy are relatively well established. Fluid emerging from the testicular limb of the vas deferens that is thick, pasty, and opaque and does not contain sperm or sperm fragments is typically considered an indication of epididymal obstruction and suggests the need for vasoepididymostomy. In some cases, however, the fluid emerging from the testicular limb of the vas deferens is noted to be clear and watery but devoid of sperm. To address the utility of performing vasovasostomy instead of vasoepididymostomy under these conditions, Taylor and Fuchs[92] evaluated 98 patients undergoing bilateral vasovasostomy performed after watery fluid was recovered from the proximal end of both vas deferentia. The authors indicated that in 82 of 98 surgical procedures, sperm were identified intraoperatively from the proximal end of at least one vas deferens. In the remaining 16 patients, however, no sperm were found in the watery fluid. Fifteen of these 16 patients had at least 2 years of follow-up. The partners of 4 of these 15 patients became pregnant following the patient's bilateral vasovasostomy. Of the remaining 11 patients, 8 men underwent postoperative semen analysis. All semen analyses demonstrated return of sperm to the ejaculate. In their conclusions, the authors indicated that men who undergo bilateral vasovasostomy after the finding of watery azoospermic fluid have a high likelihood of a successful procedure. They have yet to document a technical failure following a bilateral vasovasostomy among men in that population.

In men undergoing a vasectomy reversal, the period of time that has elapsed since the performance of vasectomy is a major determinant of the potential need for a vasoepididymostomy.

One of the most common lesions contributing to male infertility is scrotal varicocele. Although the exact pathophysiology for the varicocele effect on male infertility remains somewhat unclear, substantial attention has been devoted to elucidating this association. Shah and colleagues[93] looked at the relationship between varicocele and decreased testosterone levels in a population of infertile men. In this retrospective assessment, the records of 237 men with male factor infertility and clinical varicocele were assessed. The results of this study indicated that almost one-third of infertile patients with varicocele were hypogonadal. This phenomenon was age associated, with older men tending to have lower testosterone than younger men. The presence of varicocele was noted to be an independent predictor of lower testosterone levels. Although the exact significance of this finding in this population of patients remains to be fully defined, the link between varicocele and hypogonadism merits additional investigation.

The treatment of men whose infertility is associated with isolated teratospermia can be a challenging problem. One question that commonly arises pertains to the utility of varicocele repair in this population of patients. Macejko and coworkers[94] evaluated this question in a study of 165 patients who underwent varicocelectomy. Seventeen suffered from isolated teratospermia preoperatively. Among these 17 patients, sperm morphology normalized postoperatively

in only 3 (17.6%). Overall, no significant improvements in morphology were identified after varicocelectomy. Based on the results of this study, the authors conclude that there was no statistically significant improvement in sperm morphology after varicocele repair in men with isolated teratospermia and palpable varicoceles. [Randall B. Meacham, MD]

Peyronie's Disease

Peyronie's disease (PD) received a good deal of attention at the 2005 meeting of the AUA. First of all, the Sexual Medicine Society (SMS) dedicated some of its program to a debate about whether there have been any major advances in the knowledge and/or therapy of PD. Although all debaters presented the pros and cons of their side of the argument, there was consensus that the plaque from PD is similar to a wound that does not heal well and is characterized by excessive scarring similar to that seen with a keloid. Evidence was presented to show that the disease probably begins with fibrin from the blood becoming entrapped within the fibers of the tunica albuginea. Fibrin is a very pro-fibrotic protein and stimulates production of transforming growth factor β1, which induces the formation of myofibroblasts, and these cells then begin to secrete collagen in large quantities. Because the fibrin is trapped within the fibers of the tunica albuginea, plasmin cannot reach the fibrin to degrade it and, therefore, the stimulus for this fibrotic process (ie, the fibrin) is left unchecked.

Besides the SMS debate, the podium session on PD also introduced new information on the disease. Mulhall and colleagues[95] looked at the efficacy of intralesional verapamil given every 2 weeks for 3 months and found that in their non-controlled study, curvature was improved in 22% of patients, stable in 53%, and worsened in 25%. These efficacy values are less than those previously reported in the literature and beg the initiation of a randomized, placebo-controlled study to determine the true efficacy of these intralesional injections.

When surgery is performed to excise and/or incise the tunica in patients with Peyronie's disease, grafts are usually utilized to cover the resultant defect. The tissue-engineering group from Winston-Salem showed preliminary evidence that it may someday be possible to use tissue-engineered materials derived from collagen as such a graft, since the tunica is comprised mainly of collagen.[96] Although further work needs to done, the time is coming when we will be able to regenerate with smooth muscle cells not only the corporal tissue in patients with erectile dysfunction, but also the tunica albuginea in patients with PD.

One of the emerging facts about PD is that the mechanism that causes the plaque to form is increased collagen deposition by the fibroblasts/myofibroblasts in the tunica albuginea as the result of a pro-fibrotic stimulus. Simply speaking, there is a dysregulation of not only collagen synthesis but also collagen degradation (collagenases), an ongoing process in the tunica. Within the tunica, there are endogenous inhibitors of these collagenases called tissue inhibitors of metalloproteinases, or TIMPS, which some researchers have theorized are involved in this dysregulation of collagen synthesis/degradation in the tunica. Cole[97] showed that some of these TIMPS are increased in the plaque and the peri-plaque tunica when compared to normal tunica, suggesting that these TIMPS may play a role in the development of PD. Such elegant dissection of the ongoing biochemical processes in the plaque may someday lead to potential therapeutic regimens to modulate the synthesis/degradation pathway in patients with Peyronie's disease. One possibility would be the use of collagenases to remodel the plaque once the specific isoforms and types of collagen and collagenases in this process are identified. [Jacob Rajfer, MD]

Pediatric Urology

The pediatric urology sessions at the 2005 AUA annual meeting included 1 podium and 3 moderated poster sessions. The following summarizes some of the highlights of those sessions.

Calculi

Reisiger and associates[98] from St. Louis Children's Hospital reported on renal growth in children who had undergone various surgical treatments for stones. Renal anomalies or disease potentially affecting kidney development were excluded. Renal size was determined primarily by ultrasound. Twelve patients underwent extracorporeal shock wave lithotripsy (ESWL), 4 patients underwent percutaneous nephrolithotomy (PCNL), and 10 patients underwent ureteroscopy (URS). Average follow-up for children undergoing ESWL, PCNL, and URS was 5, 7.6, and 4.3 years, respectively. The investigators concluded that ESWL

Reisiger and associates concluded that ESWL and URS had no effect on renal growth, whereas kidneys treated with PCNL had a significant decrease in the rate of growth. It was unclear whether this was due to the disease process, the therapy, or a combination of factors.

and URS had no effect on renal growth, whereas kidneys treated with PCNL had a significant decrease in the rate of growth. It was unclear whether this was due to the disease process, the therapy, or a combination of factors.

Laparoscopy

Yee and coworkers[99] reported on their experience with robotic-assisted laparoscopic pyeloplasty using the da Vinci® Surgical System (Intuitive Surgical®, Sunnyvale, CA) in 8 patients with a mean age of 11.5 years. This was compared with an age-matched group undergoing open surgery. Robotic-assisted laparoscopic pyeloplasty had a shorter length of hospitalization and less use of pain medication. Operative times were longer than for conventional surgery. At a mean of about 15 months of follow up, all robotic procedures had been successful.

Cisek and colleagues[100] from Texas Children's Hospital presented their experience with laparoscopic pyeloplasty. They examined 27 patients with a mean age of 7.5 years. The mean operative time was 131 minutes. A stent was placed in 75% of patients and the remainder received a drain. There were no intraoperative complications. One patient developed gross hematuria and required a percutaneous nephrostomy tube due to stent occlusion. All of the patients showed improved hydronephrosis.

Woods and associates[101] reported their experience using robotic pyeloplasty in 6 patients with an average age of 11.8 years. Operative time averaged 250 minutes, with an average blood loss of 28 mL. The average hospital stay was 1.8 days. Operative intravenous pyelogram or diuretic renal scan showed improvements at an average follow-up of 8 months. There were no intraoperative complications. The authors concluded that robotic pyeloplasty can be used for children as young as 6 years of age.

Castellan and colleagues[102] reported on their experience with transperitoneal and retroperitoneal laparoscopic partial nephrectomy. They reported on 47 patients with a median age of 4.12 years who underwent partial nephrectomy. A transperitoneal approach was used in 32 patients, and a retroperitoneal approach was performed in 15 patients. The transperitoneal approach was preferred in patients less than 6 months of age when ureterectomy was performed and the kidneys were large. The retroperitoneal approach was used in older patients who required a partial ureterectomy when the kidneys were involved with an infectious process or stones. The mean follow-up was 2.4 years. The mean operative times for the retroperitoneal and transperitoneal groups were 133 and 125 minutes, respectively. Complications were seen in 13% of patients. Two of the retroperitoneal group required conversion: one to open partial nephrectomy and the other to transperitoneal laparoscopy. One patient had a postoperative leak that resolved spontaneously. In the transperitoneal group, 1 patient required a chest tube for pneumothorax. A 6-month-old developed hypertension and an additional patient required excision of the ureteral remnant due to recurrent urinary tract infections. The authors concluded that the retroperitoneal approach is superior for access to the renal pedicle. Problems occurred in the retroperitoneal approach in patients less than 6 months old since the working space was significantly reduced.

Wong and associates[103] from the University of Oklahoma reported on major laparoscopic renal surgery for infants weighing less than 10 kg. Seventeen infants, mean age 7 months with a median weight of 8.8 kg, underwent 11 nephrectomies, 4 nephroureterectomies, and 2 partial nephrectomies. Blood loss was less than 10 mL and median operative time was 138 minutes. Patients were hospitalized for 23 hours or less, except for 2 who had had additional procedures performed. The only intraoperative complication was a diaphragmatic injury successfully repaired laparoscopically followed by a pneumothorax, which resolved spontaneously. The authors concluded that major laparoscopic surgery can be safely and successfully performed in infants weighing less than 10 kg.

Peters and coworkers[104] reported on the Boston Children's Hospital experience with 24 patients undergoing robotically assisted transperitoneal extravesical antireflux laparoscopic surgery using the da Vinci system. A detrusor tunnel was created followed by closure of the muscularis over the ureter. A urethral catheter was left indwelling. The mean intraoperative times were 2.5 hours for the unilateral cases and 3.5 hours for the bilateral cases. Minor bladder leaks required catheter decompression. Of the 22 patients who underwent imaging at a mean of approximately 20 months, 18 of 20 showed no evidence of reflux on voiding cystography. No late complications have occurred.

Obstruction

The pediatric urology group at Vanderbilt University presented a retrospective study on 7 of 102 patients (7%) with failed open dismembered pyeloplasty.[105] Almost all presented with pain; 1 had increasing hydronephrosis 3 to 48 months following surgery. Four patients underwent balloon dilation and 1 underwent laser endopyelotomy. Most of these patients (6/102) required open surgery (3 ureterocalicostomies and 3 redo dismembered pyeloplasties). Dense scar was a common finding, as well as

redundant pelvis. There were 2 unrecognized crossing vessels. The authors concluded that although endoscopic margins can be attempted, most patients require open surgery for failed pyeloplasty.

Vesicoureteral Reflux

Benoit and Docimo[106] from the University of Pittsburgh presented a cost analysis of Deflux™ (dextranomer/hyaluronic acid copolymer; Q-Med AB, Uppsala, Sweden) as an alternative to open ureteral reimplantation as a treatment for vesicoureteral reflux.[9] A model was used that was previously developed to evaluate the cost of managing reflux by ureteral reimplantation. They used this model of females undergoing therapy for 5 years, but changed the therapy to subureteric injection with Deflux. The objective of the study was to determine the success rate that Deflux injection would need to achieve to have the same cost-effectiveness as surgical reimplantation. In the first scenario, Deflux injection would be substituted for ureteral reimplantation and, if Deflux failed, open ureteral reimplantation would be performed. For this to be cost-effective, the success rate for Deflux would need to be 57% for grade 1, 48% for grade 2, 21% for grade 3, 27% for grade 4, and 21% for grade 5. In the second scenario, where a failed Deflux injection would be treated with a repeat injection, the data show that the repeat injections for grades 1, 2, and 3 would need to be successful in 56%, 73%, and 92% of cases, respectively, to be equally cost-effective. There would be no equal cost-effectiveness for grades 4 and 5, even if the success rate were 100%. They concluded that Deflux is likely more cost-effective than ureteral reimplantation for all grades of reflux, but once the first injection fails a repeat Deflux will be more cost-effective than surgical reimplantation for only grade 1 reflux.

Elmore and colleagues[107] in Atlanta reported a retrospective study examining their success rates using endoscopic therapy with Deflux following a second injection in patients with primary reflux. Of the 42 children (mean age 5 years) undergoing a second Deflux injection, complete data are available for 34 patients. This group had a mean grade of 2.6 prior to the initial therapy; following the first injection the mean grade was 2.3. A second injection resolved reflux in 85% of patients. There is no significant difference for those with reflux grades 1, 2, or 3. The authors concluded that the second Deflux injection after the initial failed procedure has high success rates.

Deflux™ is likely more cost-effective than ureteral reimplantation for all grades of reflux, but once the first injection fails a repeat Deflux will be more cost-effective than surgical reimplantation for only grade 1 reflux.

Cryptorchidism

Nguyen and associates[108] at the Children's Hospital of Philadelphia examined fertility potential in the cryptorchid male using spermatozoal gene expression microarray analysis. They utilized microarray analysis to identify significant differences in spermatozoal gene expression patterns between adolescent males with a history of surgically treated cryptorchidism and normal controls. Cryptorchidism males (8 unilateral, 4 bilateral) had median semen volumes that were not significantly different from those of the controls. Median sperm density was markedly decreased in the cryptorchid group. The authors identified 47 genes differentially expressed in the 2 groups. Of these, 42 were underexpressed in the cryptorchid samples. Two genes were significantly affected in the cryptorchid boys: expression of *Tpx-1*, which is the testis-specific spermatogenic-Sertoli cell adhesion gene, was decreased, and an apoptotic gene, *TNFAIP3*, was highly overexpressed.

[Ellen Shapiro, MD, FACS, FAAP]

Bladder Cancer

Presentations on bladder cancer at the 2005 annual meeting of the AUA covered many aspects of the disease, including molecular markers, detection and screening, diagnosis and prognostication, superficial disease, muscle-invasive disease, and advanced disease. Some of the many outstanding abstracts are highlighted here.

Molecular Markers

The search continues for better tumor markers to improve the rate of detection of transitional cell carcinoma (TCC) of the bladder in larger populations and to predict the possibility of disease recurrence, including progression and metastasis. Steinberg and associates[109] evaluated the mitotic kinase-encoding gene Aurora A as a potential biomarker for bladder cancer. Aurora A gene amplification was found to be ubiquitous in bladder cancer and was associated with increased chromosome copy number, tumor aneuploidy, and aggressive clinical features.

Moore and associates[110] evaluated the level of expression of COX-2 in patients with superficial bladder cancer and determined risk in these patients. A total of 213 patients with superficial bladder cancer were evaluated by immunohistochemical analysis with an anti-COX-2 monoclonal antibody. Overall, 24% of tumors

demonstrated COX-2 expression. Expression of COX-2 was associated with tumor grade, stage and number of tumors, and a shorter recurrence-free survival. The authors commented that COX-2 (implicated in inflammation and tumorigenesis) is associated with a high-risk group of patients with superficial bladder cancer. Furthermore, from these findings, the authors suggested that it would be reasonable to investigate the application of a nonsteroidal anti-inflammatory drug (NSAID) in the prevention of superficial bladder cancer.

Bakkar and colleagues[111] previously reported that *FGFR3* mutations were associated with tumors having good prognosis and correlated with low proliferation status, and *TP53* mutations correlated with aggressive tumors. In the present study, the authors analyzed the mutational status of *FGFR3* and *P53* by denaturing high-performance liquid chromatography (DHPLC) and sequencing in 56 patients with T1G3 bladder cancer treated by transurethral resection and who had received at least 6 bacillus Calmette-Guérin (BCG) instillations, and related the findings to clinical outcome. The authors reported that *FGFR3*, but not *TP53*, mutations were associated with decreased tumor progression and increased cancer-specific survival in patients with T1G3 tumors.

Matsuyama and colleagues[112] evaluated centrosome hyperamplification (CH) by immunohistochemistry in 50 bladder cancers. CH-positive cases (CH+) were defined as those having more than 5% of cells with 3 or more centromeres per cell. Patients with CH+ tumors had a significantly lower recurrence-free and progression-free survival rate. CH+ was the strongest predictor for tumor recurrence in non-muscle-invasive (pTa and pT1) bladder cancer, based on multivariate analysis.

Patry and associates[113] evaluated tissue factor (TF)—a transmembrane glycoprotein responsible for initiating the extrinsic pathway of blood coagulation that plays a role in cancer growth, metastasis, and angiogenesis—as a prognostic marker for patients with muscle-invasive bladder cancer treated by radical cystectomy. TF expression was evaluated in a tissue microarray constructed from 217 patients with muscle-invasive bladder cancer. In patients without lymph node metastasis (N0), those with TF-positive tumors had a 2.7 times higher risk of dying from their bladder cancer. These authors suggest that this cohort of patients may potentially benefit from adjuvant therapy.

In patients with muscle-invasive bladder cancer without lymph node metastasis, those with tissue factor–positive tumors had a 2.7 times higher risk of dying from their bladder cancer.

Harris and coworkers[114] performed immunohistochemistry staining on a tissue microarray consisting of samples from 251 TCC bladder cancers, using antibodies to pAkt, PTEN, and L-plastin. The tumor types examined included nonpapillary invasive G3, papillary invasive G3, papillary noninvasive G3, and papillary noninvasive G2. Expression of pAkt was higher in papillary noninvasive G2 tumors than in nonpapillary invasive G3 tumors. L-plastin exhibited higher expression in papillary noninvasive tumors than in nonpapillary invasive G3. Cytoplasmic PTEN expression and nuclear PTEN expression were lowest in nonpapillary invasive tumors compared with all other tumor types examined. There was a moderate correlation between pAkt and L-plastin expression.

Myers-Irvin and Getzenberg[115] examined the expression pattern of a novel bladder cancer–specific nuclear protein, BLCA-1. This protein was detectable in the affected tissues from patients with bladder cancer but not in the normal adjacent regions of the bladder or in normal donor bladder tissue. Importantly, this protein was also detectable in the urine of patients with bladder cancer, including 22 of 27 urine samples from patients with bladder cancer, but in only 6 of 46 so-called normal patients. This resulted in a sensitivity of 82% and specificity of 87%. This study is unique in that it identifies a novel marker (BLCA-1) that may help selectively evaluate both tissue and urine from bladder cancer patients and from normal, nonmalignant cases. As with the fluorescent in situ hybridization (FISH) or other molecular assays, this marker may enhance sensitivity and specificity in detection of bladder cancer and in the future may be employed in conjunction with urine cytology.

Methods based on gene arrays, which screen for differential expression of thousands of genes, have identified large numbers of new, potentially important prognostic markers for patients with bladder cancer.

Methods based on gene arrays, which screen for differential expression of thousands of genes, have identified large numbers of new, potentially important prognostic markers for patients with bladder cancer. The evaluation of protein expression

in a high-throughput tissue array is a natural extension of the efforts in molecular staging. Several abstracts were presented on this topic. Wu and colleagues[116] reported on the differential expression of genes as a function of bladder cancer progression and metastasis by profiling a progressive bladder cancer lung metastasis model and primary human bladder tumors of varying stage, using the Hu133A array (Affymetrix, Santa Clara, CA). Chromosome 20 was found to harbor a higher than usual number of gene expression changes, and chromosome 17q was found to have a region with an especially high density of differentially regulated genes as a function of lung metastasis, suggesting that genes on these 2 chromosomes are likely to be involved in human bladder cancer lung metastasis. Sanchez-Carbayo and associates[117] performed gene transcript profiling of 77 invasive bladder tumors, using the U133A oligonucleotide microarrays (Affymetrix). The differential protein expression of selected molecular targets was validated by immunohistochemistry on a separate cohort of 294 patients with bladder tumors, with samples contained on tissue microarrays. More than 200 genes were identified to be differentially expressed between patients with and without lymph node invasion. Molecular pathway analyses revealed 2 main pathways characteristic of lymph node invasion, which integrate reorganization of extracellular matrix and the cytoskeleton. MMP2 and synuclein expression were associated with stage, tumor grade, lymph node status, and overall survival.

Detection and Screening

Tumor-associated trypsin inhibitor (TATI) has previously been identified as one of the genes that may be involved in the early phases of urothelial tumor development. Shariat and associates[118] evaluated whether TATI would aid in the detection of TCC of the bladder and compared its diagnostic performance with that of urinary nuclear matrix protein 22 (NMP22® BladderChek® Test; Matritech, Newton, MA) and cytology. Urinary TATI levels were significantly higher in patients with TCC ($n = 96$) than in control subjects. Higher levels of TATI were associated with positive cytology, higher NMP22 levels, and invasive tumor stage. Furthermore, TATI, NMP22, and cytology were all independently associated with bladder cancer after adjustment for age.

The coordinated use of urine cytology and UroVysion (Vysis®; Abbott Laboratories, Downer's Grove, IL) FISH in diagnosing recurrent and new urothelial carcinoma was reported by Shappell and colleagues.[119] This was a prospective series of 7529 consecutive urine cytologies paralleled by 479 FISH assays (138 FISH only and 341 with cytology). There was a strong correlation between cytology diagnoses and FISH results. In 289 cases with a history of urothelial carcinoma, FISH was positive in 10%, 41%, 65%, and 100% of cases with negative, atypical, suspicious, and positive cytology, respectively. In 188 cases without a history of urothelial carcinoma (> 90% hematuria), FISH was positive in 0%, 21%, 48%, and 100% of cases with negative, atypical, suspicious, and positive cytology, respectively. Based on these results, the authors concluded that samples with negative or positive cytology may not need more costly molecular analysis, whereas samples with the cytology diagnoses of atypical or suspicious may benefit from a more definitive analysis by FISH.

Katz and Messing[120] evaluated whether a point-of-care proteomic test (NMP22 BladderChek Test) that measures NMP22 in voided urine could enhance detection of bladder cancer in high-risk or symptomatic patients. This study included 23 academic, private practice, and veterans' facilities in multiple states. A total of 1331 patients at risk for bladder cancer (history of smoking, or symptomatic hematuria or dysuria) were evaluated with urine cytology and NMP22 prior to cystoscopy. Cystoscopy with biopsy was defined as the reference standard, and the performance of NMP22 was then compared with voided urine cytology for bladder cancer detection. A total of 79 patients were diagnosed with bladder cancer, of which 10 cases were muscle invasive. NMP22 was positive for 9 of the 10 (90%) muscle-invasive tumors, whereas cytology was positive for only 2 (20%). The NMP22 test detected more than 3 times as many tumors as cytology and identified 32 bladder cancers that were missed with cytology. The overall accuracy of NMP22 was 84%, and the combination of NMP22 and cystoscopy detected 95% of the malignancies, compared with 90% for initial cystoscopy alone. This study supports the use of noninvasive measure of the urine with NMP22 in combination with cystoscopy as a means of evaluating patients at high risk for bladder cancer. Importantly, the results of the test are available immediately during the patient's visit, and the cost of NMP22 BladderChek was less than half that of voided cytology.

Sandhu and associates[121] evaluated a group of 100 patients with a diagnosis of bladder cancer following a previous prostate cancer diagnosis to determine whether bladder cancer diagnosed after prostate radiation therapy is clinically different from bladder cancer diagnosed after prostate cancer not previously treated with radiotherapy. Bladder cancer diagnosed after radiotherapy for prostate cancer in this series was high grade (97%) and more commonly muscle invasive

(52%) than bladder cancer diagnosed in patients with a history of prostate cancer not previously treated with radiation therapy. This important study underscores the potential for various pelvic malignancies (rectal and bladder) following definitive therapy for prostate cancer. The authors correctly comment that patients with a history of prostate cancer who have been treated with radiation therapy must be carefully monitored for bladder cancer, which, if it develops, is aggressive in nature.

Singh and associates[122] investigated the risk of developing a secondary malignancy of the bladder or prostate following a previous diagnosis of prostate or urothelial cancer. The incidence of lung, colon, and renal cancers was also analyzed in these patients. The standardized incidence ratio was used to evaluate the reported cases of cancer in the Upstate male population from the New York State Cancer Registry between 1996 and 2003. In short, patients with prostate cancer were found to have a higher incidence of TCC, and patients with bladder cancer were observed to have a higher incidence of prostate cancer. The risk for other cancers was not significantly increased. This study highlights the fact that doctors must carefully follow up bladder and prostate cancer patients and understand the potential risk of another malignancy developing in these patients.

Meissner and Studer[123] evaluated the application of intravenous urography (IVU) following cystectomy and ileal diversions for upper tract tumor recurrences. This retrospective study evaluated 407 patients over 19 years (median follow-up 43 months). Overall, 12 patients (2.9%) developed an upper tract recurrence. The median time from cystectomy to upper tract recurrence was 31 months (range 12 to 61 months). Five of the 12 patients were diagnosed with routine IVU, 5 were diagnosed because of hematuria, and 2 patients because of pain. Of the 5 patients diagnosed with IVU, 4 died of metastatic disease. The outcomes of the other 7 symptomatic patients were not reported. The authors commented that the incidence of upper tract tumors following cystectomy is low (3%), and over half of these patients will present with symptoms. They suggested that the cost and radiation exposure from the IVU study were not clearly beneficial to the patients, and recommended that follow-up strategies should be reconsidered and IVU reserved for high-risk patients or those with abnormal renal ultrasound. This study raises several important issues about the follow-up of patients with a history of bladder cancer and radical cystectomy. Granted, the incidence of upper tract tumors may be low (3%-5%) in this cohort; however, a recurrence can be potentially lethal. All attempts should be made to diagnose early, when there is a better chance of curing the disease. Risk factors in this group are reported to include tumor multifocality, carcinoma in situ of the bladder or distal ureter, and locally advanced disease, which represents a significant portion of all patients undergoing cystectomy. A more diligent approach using urine cytology and/or other urinary molecular markers might be considered for these patients, and more frequent and/or alternating upper tract studies (ie, CT scan) on a 6-month basis might be entertained.

Schmidbauer and associates[124] compared the results of detecting bladder cancer using flexible and rigid cystoscopies, in white and blue light modes. A total of 92 patients with high-risk bladder tumors had 50 mL of hexyl-aminolevulinate (HAL) instilled intravesically 1 hour prior to the procedure, and cystoscopy (both rigid and flexible) was then performed using a Combilight PPD™ system (Richard Wolf, Knittlingen, Germany) that allows for both white and blue light inspection. Initially, all suspicious lesions were mapped with the rigid and flexible cystoscopes, and with white and blue light. All lesions were then biopsied or resected. The lesion detection rate was then determined for each method. The authors noted that flexible cystoscopy with HAL demonstrated a similar detection rate to rigid cystoscopy with HAL. The detection rate was improved with HAL compared to standard rigid and flexible cystoscopy. These findings were particularly pronounced in patients with carcinoma in situ (CIS) with the application of HAL. These data provide additional evidence to a growing body of work to suggest that fluorescence cystoscopy is an important tool in the evaluation of patients with bladder tumors.

Wu and associates[125] presented a study on the influence of dietary carotenoids and genetic instability in bladder cancer development. The authors assessed 423 patients with bladder cancer and 467 healthy controls from an ongoing bladder cancer case-control study. The self-reported intake of carotenoids was determined and genetic instability (DNA damage) assessed by comet assay. The association of carotenoid intake and genetic instability with bladder cancer risk was then determined. There was a significantly lower reported intake of carotenoids in patients with bladder cancer compared with controls. In fact, there was an inverse relationship between increasing levels of carotenoids and bladder cancer risk. DNA damage was also significantly higher in bladder cancer patients than in controls. When analyzed jointly, high DNA damage and low carotenoid intake was associated with the highest risk. The study suggests the potential preventative role of carotenoid in

bladder cancer, particularly in high-risk individuals susceptible to DNA damage.

Staging and Prognostication

Several interesting abstracts on prognostic indicators following radical cystectomy were presented. Lymphovascular invasion (LVI) has previously been recognized as a potentially important pathologic parameter. Lee and associates[126] evaluated the role of LVI on a cohort of 117 patients with an initial clinical diagnosis of T1 (invasion of the lamina propria) bladder cancer who underwent radical cystectomy, in order to determine whether this pathologic marker may better guide patients with lamina propria invasion toward an early cystectomy. In the group studied, 21% had progressed to muscle invasion (cT2) and 79% had cT1 tumors at cystectomy. Multiple variables were evaluated, including LVI, carcinoma in situ, tumor grade, as well as surveillance time and certain demographic characteristics. Histologic review demonstrated that 30% of patients had LVI in the tumor specimen. Understaging was observed in 81% of patients with LVI, significantly higher than in patients without LVI. On multivariate analysis, LVI, increasing age, and tumor grade were retained as predictors of poorer disease-specific survival (DSS). Other factors including associated CIS, gender, and surveillance time were not significant. The authors suggested that although LVI may not commonly be seen in patients with cT1 tumors, when present this pathologic marker is associated with significant clinical understaging and worse survival following cystectomy. Patients with LVI and cT1 tumors may benefit from an earlier and more aggressive form of therapy such as radical cystectomy.

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Kamat and colleagues[127] presented 2 abstracts on micropapillary TCC of the bladder, an uncommon and highly aggressive variant. These authors retrospectively reviewed the records of 100 consecutive patients, evaluated between 1989 and 2004, who had TCC of the bladder with micropapillary features. Of these patients, 44 had non-muscle–invasive disease at presentation. The overall 5- and 10-year disease-free survival (DFS) was 40% and 13%, respectively, and the overall 5- and 10-year DSS was 62% and 34%, respectively, for this cohort of patients. Intravesical therapy was attempted in 27 patients and at a median of 8 months after therapy, 18 (67%) had progression of disease ($\geq$ cT2) and 6 (23%) had developed metastatic disease. At a median follow-up of 45 months, only 5 of the 44 patients (12%, all T1) remained free of disease with an intact bladder. Of the 29 patients who proceeded to cystectomy, median DSS for the 17 patients with progression to muscle invasion was 51 months, whereas the 12 patients that underwent cystectomy prior to stage progression did not reach median DSS. These authors therefore recommend that radical cystectomy be performed for non-muscle-invasive micropapillary TCC prior to progression. The same authors also analyzed a cohort of 63 patients with micropapillary TCC who underwent cystectomy, including 32 who received neoadjuvant chemotherapy.[128] The overall 5- and 10-year DSS was 50% and 26%, respectively. Of the 55 patients who had surgically resectable disease initially, 23 received neoadjuvant chemotherapy, and 32 were treated with initial cystectomy, with no significant difference in stage distribution between the 2 groups. The pathologic stage was higher than the clinical stage in 65% of patients treated with initial cystectomy. The median cancer-specific survival (CSS) for the neoadjuvant group was 43 months with a DFS of 32% at 5 years. A pT0 tumor was seen in 39% of these treated patients, with all of those disease free with a median follow-up of 20 months. Of the 32 patients undergoing initial cystectomy, the CSS had not been reached and the DFS was 78% at 5 years. Clinical understaging was seen in 65% of the patients undergoing initial cystectomy. Importantly, of the 32 patients undergoing cystectomy initially, 17 were then treated with adjuvant chemotherapy, which did not seem to improve the DFS or the CSS.

Predictive nomograms following treatment for bladder cancer were presented by 2 groups. The International Bladder Cancer Nomogram Consortium developed a bladder cancer–specific nomogram predicting survival following radical cystectomy, derived from an international database consisting of 5483 patients.[129] Death due to any cause occurred in 38% of patients. The bootstrap-corrected concordance index was 0.722. Multivariate analysis found that pathologic stage, nodal status, histologic cell type, grade, age at cystectomy, and preoperative radiotherapy were significant risk factors associated with death following radical cystectomy, whereas perioperative chemotherapy or previous intravesical chemotherapy were not. Karakiewicz and colleagues[130] constructed a nomogram to predict patient-specific relapse probability following radical

cystectomy, based on 958 patients from 3 institutions. Relapse occurred in 29.2% of patients. Mean and median times to relapse were 35.5 and 22.6 months, respectively. The 24-, 60-, and 96-month actuarial probabilities of relapse-free survival were 73.1%, 65.6%, and 57.5%, respectively. The 3 most informative multivariate predictors were adjuvant radiotherapy, adjuvant chemotherapy, and neoadjuvant chemotherapy, which identified patients at high risk of relapse. The nomogram bootstrap-corrected predictive value was 0.799.

Superficial Disease

Sachs and associates[131] reported the results of a 5-year, prospective, randomized trial evaluating recurrence rates and tumor progression with standard light cystoscopy compared with 5-aminolevulinic acid (ALA) fluorescence techniques, following transurethral resection (TUR) in patients with superficial bladder cancer. A total of 115 patients were randomized to undergo resection by 1 of the aforementioned techniques. A second look (TUR) was performed 6-8 weeks later, with subsequent routine follow-up. The authors found the rate of tumor recurrence and tumor progression was significantly decreased in the ALA group. Furthermore, a cost analysis found a strong economic advantage to the ALA group because of the reduced number of TURs required. This is another study lending support, both clinically and economically, to the application of fluorescence cystoscopic evaluation for patients with bladder cancer.

Lerner and associates[132] reported the results of a randomized chemoprevention trial with fenretinide in patients with non-muscle–invasive bladder cancer. Fenretinide is a potent inducer of apoptosis, with a favorable toxicity profile, that has been shown to have clinical activity with other types of malignant tumors. This phase III, randomized, chemoprevention trial evaluated the efficacy, mechanism of action, and toxicity profile of fenretinide in the prevention of tumor recurrence in patients with non-muscle–invasive bladder cancer (Ta, Tis, or T1) following TUR with or without BCG therapy. A total of 149 patients were enrolled, with 133 of these evaluable for the recurrence endpoint. In short, although the drug seemed to be administered safely, with a low toxicity profile, the study was discontinued by the data monitoring committee as a result of the low likelihood of detecting a significant reduction in the recurrence rate in the treated fenretinide arm.

McKiernan and associates[133] reported the results of a phase I trial of intravesical docetaxel in the treatment of superficial bladder cancer refractory to standard intravesical agents. Six weekly instillations of docetaxel were administered to 18 patients with recurrent Ta, T1, and Tis tumors that had failed to respond to at least 1 intravesical agent. Overall, 78% of patients completed the trial. Fifty-seven percent (8/14) of patients who completed the trial had no evidence of disease at their post-treatment cystoscopy and biopsy. No patient developed systemic absorption of the drug, or grade 3 or 4 dose-limiting toxicities. Grade 1 or 2 toxicities were observed in 68%, with the most common being dysuria. At a median follow-up of 5.6 months, all patients with a complete response remained free of disease, while none of those with a recurrence developed progression. This study of a novel intravesical agent (docetaxel) with a low toxicity profile and no systemic absorption suggests that future phase II trials for efficacy should be considered. These findings are encouraging, as second-line intravesical agents for superficial bladder cancer are clearly needed to better treat those patients who fail to respond to initial intravesical therapy.

Maymi and O'Donnell[134] evaluated the influence of prior intravesical treatment on the effectiveness of BCG plus interferon (IFN) in patients with CIS of the bladder. A total of 231 patients with CIS were evaluated, including 106 BCG-naive patients and 125 patients who had been treated previously with BCG but failed to respond to initial therapy (BCG-failures). The naive group received a 6-week course of standard-dose BCG plus IFN, followed by 3-weeks' maintenance of reduced BCG dose plus IFN at 3, 9, and 15 months. Patients not responding to previous therapy were treated with a similar regimen but had reduced doses of BCG at re-induction. The complete response rates for the BCG-naive and BCG-failures at 3 months (76% and 70%, respectively) and 6 months (76% and 66%, respectively) were similar for both groups. However, at 24 months there was a significantly lower disease-free rate in patients failing 2 or more courses of BCG (23%), compared with those failling 1 course (57%) and with BCG-naive patients (60%). Patients never free of the disease (highest-risk group) demonstrated the worst outcome compared with those who had a recurrence within the first year (intermediate-risk group) and after the first year (lowest-risk group). No clinical differences were observed in outcomes in the subgroups of pure CIS compared to CIS with coincident bladder tumors. The authors commented that these data demonstrate the efficacy of BCG plus IFN therapy as initial and salvage therapy for patients with CIS. Importantly, they identified patients at high risk, including those who have failed 2 or more previous BCG treatments, and those with early or persistent CIS. It is these patients who may benefit

from an early, more definitive form of therapy.

Sylvester and associates[135] reported the results of a meta-analysis of the published data from randomized clinical trials comparing the efficacy of intravesical BCG with intravesical chemotherapy in patients with CIS of the bladder. In this study, 9 randomized trials were identified that included 700 patients with CIS. Variables in this study included patients with concomitant papillary tumors, comparison with different chemotherapy agents, the BCG strain, and the fact that 6 trials had some form of maintenance therapy of BCG. With a median follow-up of 3.6 years, 48% of patients receiving BCG had no evidence of disease, compared with 26% on intravesical chemotherapy. BCG was superior to mitomycin C if maintenance therapy of BCG was instituted. The authors also found a 26% reduction in the risk of progression for patients receiving BCG, a similar incidence (27%) to that found in a previous meta-analysis of 4800 patients with superficial bladder cancer. The authors correctly commented that BCG seems to significantly reduce the risk of treatment failure compared with intravesical chemotherapy agents and should be considered the intravesical agent of choice for CIS of the bladder.

Muscle-Invasive and Advanced Disease

Touijer and associates[136] reported on the effect of body mass index (BMI) on the quality of surgery performed and the morbidity of radical cystectomy in patients with bladder cancer. A total of 141 patients were evaluable: 27% of patients were normal weight (< 25 kg/m^2), 40% were overweight (25-29.9 kg/m^2), and 33% were morbidly obese (> 30 kg/m^2). There was no difference in the quality of surgery in terms of the extent of the lymphadenectomy, nodal ratio, or the number of nodes removed. Interestingly, although positive surgical margin rates decreased significantly with increasing BMI (normal, 18.4%; overweight, 12.5%; and obese, 2.2%), this did not translate into lower local recurrence rates. Obese patients were more likely to have urinary complications or require a return to the operating room. Operative times were longer with increasing BMI, but there were no significant differences in estimated blood loss or transfusion rates. It is clear that radical cystectomies can be challenging surgical operations in patients with an increased BMI and have a slightly higher complication rate, but this should not preclude patients from a timely and properly performed cystectomy for bladder cancer.

Kassouf and coworkers[137] reported on their experience of 31 patients with viable tumor in lymph nodes following neoadjuvant chemotherapy. The overall and recurrence-free 5-year survival rates were 38% and 10%, respectively. Pathologic T stage, total number of lymph nodes removed, number of positive nodes, and lymph node density did not correlate with overall and recurrence-free survival (RFS). The use of adjuvant chemotherapy was the only factor that correlated with improved RFS in multivariate analysis. Median RFS for patients who received adjuvant chemotherapy was 15.6 months, versus 4.8 months for those who did not. This same group evaluated the relevance of lymph node density in a contemporary series of 111 patients with lymph node–positive disease.[138] The incidence of positive lymph nodes did not significantly increase with higher pathologic T stage. The median number of lymph nodes removed was 12 (range 1 to 37), while the median number of positive lymph nodes was 2 (range 1 to 10). Five-year overall survival, DSS, and RFS rates were 41%, 53%, and 34%, respectively. Lymph node density above 25% significantly correlated with DSS and RFS. Patients with a lymph node density of 25% or less had a 43.1% 5-year RFS, compared with 16% for those with a lymph node density above 25%. However, the total number of lymph nodes removed at surgery or the number of nodes involved with tumor was not prognostic. Reese and associates[139] reported that positive lymph nodes were a poor prognostic indicator and that there was no difference in survival when stratifying patients according to number of positive lymph nodes, total number of nodes, or lymph node density. The estimated 2- and 5-year DFS for 55 patients with node-positive disease was 41.3% and 27.6%, respectively. The estimated 2- and 5-year DSS was 52.8% and 33.8%, respectively, and the estimated 2- and 5-year overall survival was 44.5% and 23.3%, respectively.

Hautmann and associates[140] reported the results of 788 patients treated with radical cystectomy only (no adjuvant or neoadjuvant chemotherapy) for muscle-invasive or recurrent superficial high-grade bladder cancer. Increasing pathologic stage, lymph node status, and preoperative hydronephrosis were important risk factors for tumor recurrence in this surgical group. Local recurrence was first seen in 9% of patients, with distant metastases seen in 17%. Urinary tract recurrences were seen in 3%. The authors noted a significantly increased risk of recurrence when comparing superficial muscle-invasive tumors (pT2a) and deep muscle-invasive tumors (pT2b). Unfortunately, it is not clear whether lymph node status was controlled for in these groups. Regardless, this uniformly treated group of patients with bladder cancer had excellent clinical

results, with good local control of the bladder tumor, and provides outcomes with which other forms of therapy can be compared.

Rozet and associates[141] reported their results of laparoscopic-assisted radical cystectomy for bladder cancer in 72 patients. The median operative time was 280 minutes, with a median estimated blood loss of 590 mL and a transfusion rate of 5%. There were no conversions to an open technique, with all negative margins and no trocar site metastases. The authors commented that this approach is feasible with decreased bleeding and less postoperative pain. They acknowledged that longer follow-up is required to confirm the oncologic outcomes. This report suggests that a laparoscopic technique is a viable approach to the treatment of bladder cancer. However, the extent of the lymphadenectomy and the form of urinary diversion are not given in the abstract. These factors clearly have oncologic and quality-of-life implications and are probably more important than such short-term indices as duration of surgery, transfusion rate, and postoperative pain.

Wiessner and associates[142] studied the factors contributing to the development of a postoperative ileus in patients undergoing radical cystectomy. A total of 302 patients were evaluated over an 8-year period of time. Ileus was defined as the absence of bowel sounds and defecation for more than 4 days postoperatively. A multivariate analysis was performed evaluating: American Society of Anesthesiologists (ASA) score (comorbidity status), age, gender, duration of surgery, type of diversion, transfusion requirements, postoperative complications, and method of pain relief. In multivariate analysis, age, gender, type of urinary diversion, and previous abdominal surgery were not significant variables, whereas ASA score above 2, BMI, type of anesthesia, and surgical complications were significant factors that contributed to a postoperative ileus in this cohort of patients. The strongest predictor for the duration of a postoperative ileus was the type of pain relief administered. Patients undergoing an epidural analgesia had the lowest risk of a postoperative ileus in this study.

In a study by Wiessner and associates, the strongest predictor for the duration of a postoperative ileus for radical cystectomy was the type of pain relief administered. Patients undergoing an epidural analgesia had the lowest risk of a postoperative ileus in this study.

Simon and associates[143] evaluated their experience of 90 patients who had received BCG prior to radical cystectomy. With a mean follow-up of 32 months, 19% of patients died of bladder cancer. There was no apparent difference in the DSS when comparing patients treated with 1 or more courses of BCG intravesical therapy. In addition, there was no apparent difference when comparing early cystectomy (within 1 year of BCG treatment) and a delayed cystectomy. As expected, DSS correlated with the pathologic stage. The authors note that, for those patients undergoing cystectomy for bladder cancer previously treated with BCG, the 5-year DSS is only 69%, and acknowledge that it may be difficult to predict which patients may be best treated with an early cystectomy or with a trial of BCG. This study underscores the continued need to better define risk assessment factors for patients with superficial bladder cancer, including clinical, pathologic, and even molecular markers. There is clearly a group of patients with this disease that are best treated with an early cystectomy.

Tai and associates[144] compared gender differences in patients with bladder cancer undergoing radical cystectomy and evaluated the pathologic characteristics and the postoperative outcomes in these 2 groups. A total of 141 women and 232 men were evaluated. Minor complications were more common in men, but the rates of major complications were not different. Tumor grade, stage, and nodal status were not significantly different between the groups, but women had more positive surgical margins (18% vs 10%). Positive margins were more commonly seen in non-TCCs of the bladder. Recurrence free survival for TCCs was worse for women than men in this series. Although presentation and pathologic stage do not seem to be different in men and women, the data from this series suggest that women undergoing cystectomy for bladder cancer have worse outcomes than do men.

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Kidney and Urothelial Cancers

Molecular Markers and the Scientific Foundation for Targeted Kidney Cancer Therapy

Work on molecular markers in kidney cancer was presented at this year's AUA annual meeting. These findings are relevant in that they may affect the various targeted therapies for renal cell carcinoma (RCC). Several groups focused on characterizing the protein expression of pathways downstream of the tyrosine kinase receptors that include the epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and

platelet-derived growth factor (PDGF) receptor families.

Pantuck and coworkers[145] presented data on the protein expression of the mammalian target of rapamycin (mTOR) pathway in the primary RCC specimens from 417 patients. The authors reported that a significant percentage of clear cell RCC tumors (24.8%) and tumors with sarcomatoid features (34.4%) had loss of PTEN expression. In addition, pAkt staining frequency was greatest in collecting duct (88.9%) followed by clear cell (57.5%) tumors, which suggests pathways of activation other than PTEN loss. S6 kinase, an end product of the mTOR pathway, was highly expressed by tumors with sarcomatoid features (61.1%) and clear cell (40.8%) tumors, and increased expression was associated with high-stage and high-grade tumors. Expression of hypoxia-inducible factor-1 alpha (HIF-1α) was highest in clear cell tumors. PTEN expression was also correlated with expression of pAkt ($P = .028$) and HIF ($P < .0001$).

Merseburger and associates[146] also evaluated the mTOR pathway, using Western blot analysis and real-time polymerase chain reaction (PCR), in 12 RCC specimens and their corresponding normal tissue samples; an additional 100 specimens underwent immunohistochemical evaluation to detect levels of expression of PTEN and p27/Kip1. In contrast to a few previous reports, the authors found that higher levels of p21 and p27/Kip1 were expressed in some RCC specimens than in the corresponding normal samples. However, expression levels of proteins in the PKB/Akt pathway in the tumor samples varied independently from histologic grade and tumor stage, underscoring the importance of understanding molecular marker expression to guide patient selection for targeted therapies.

Leppert and colleagues[147] presented expression data of the VEGF angiogenesis family in RCC. This study of 340 clear cell and 42 papillary primary RCC specimens demonstrated significant expression of VEGF-A and its tyrosine kinase receptors VEGFR-1 and VEGFR-2 in both histologic types of RCC. These data imply that patients with papillary-type RCC may benefit from emerging therapies targeting the VEGF angiogenesis pathway.

Rioux-Leclercq and coworkers[148] prospectively examined VEGF staining in 50 clear cell RCC specimens. They reported a significant correlation between VEGF-A expression by immunohistochemistry and circulating levels of VEGF-A isoforms. These levels correlated with clinical factors such as T stage, Fuhrman grade, and the presence of tumor necrosis, highlighting the importance of the von Hippel-Lindau (VHL)/hypoxia-inducible/VEGF axis in clear cell RCC.

Junker and colleagues[149] identified CD70, a transmembrane protein from the tumor necrosis factor (TNF) family that represents the ligand for CD27, as a novel, specific marker of clear cell RCC. In their series of 68 tumors of different histopathologic subtypes that were investigated by immunohistochemistry, the authors identified a high level of CD70 expression in all 41 clear cell RCC tumors, with no evidence of expression in normal tissue.

Several presentations further characterized the role of the VHL tumor suppressor protein and downstream molecular targets. Gong and colleagues[150] found the incidence of VHL mutations in Chinese sporadic clear cell RCC to be 51.9% by PCR when comparing 77 paired normal and tumor tissue specimens. The positivity of VEGF staining was 77.2%, and the positivity of HIF-2α staining was greater than that of HIF-1α staining (80.5% vs 60.2%; $P < .01$). Furthermore, the positivity of HIF-1α, HIF-2α, and VEGF staining in the cases of VHL gene mutations was higher than that in non-mutations (97.5%, 92.5%, and 92.5%, respectively, vs 32.4%, 67.6%, and 64.9%, respectively; $P < .01$). RCC lesions in patients with a VHL gene mutation were also found to have an increase in microvessel density (MVD).

Fergelot and associates[151] reported on the ability to screen for VHL mutations using denaturating high-performance liquid chromatography (DHPLC). This technique was correlated with PCR analysis of DNA sequencing to identify VHL mutations in 16 RCC specimens. This technology demonstrates the suitability of DHPLC for high-throughput mutation scanning of VHL abnormalities in sporadic RCC. Furthermore, VHL mutations seem to be associated with a less aggressive tumor profile as well as an improved initial outcome.

VHL mutations seem to be associated with a less aggressive tumor profile as well as an improved initial outcome.

Shinojima and coworkers[152] reported their findings that, in 4 of 9 RCC cell lines studied, the VHL gene was inactivated due to frame-shift mutation or hypermethylation, and these were all associated with loss of HIF-1α expression. In these VHL mutant cell lines, HIF-2α was shown to regulate the production of VEGF-A, whereas HIF-1α controls VEGF production in wild-type cell lines. These findings may have important implications in choosing which molecule to target for RCC therapy.

Gene arrays were also a focus of attention at this year's meeting. Parker and colleagues[153] reported the

differential gene expression between 11 low-grade and low-stage tumors and 9 metastatic tumor lesions. Using the Affymetrix chip with unsupervised clustering analysis, the authors identified 34 mRNA differences between the clear cell RCC samples from patients with good versus poor outcomes. These results were validated using real-time, reverse-transcription PCR on an independent cohort of patients. Zhao and associates[154] analyzed cDNA array data in a training set of 119 tumors and evaluated these data in a second set of 59 lesions. They found more than 2700 clones with a 3-fold difference among patients. Further refinement of these candidate markers revealed that as few as 35 clones could accurately predict DFS. Gottardo and coworkers[155] reported their application of micro-RNA arrays in RCC. Micro-RNAs are a class of small noncoding RNA genes thought to regulate gene expression, although their role in oncogenesis remains unknown. By evaluating 327 probes in 20 kidney cancer specimens and 25 bladder cancer specimens, the authors identified 4 candidate probes with significantly different expression in kidney cancer specimens and a different spectrum of 10 probes for the bladder cancer specimens. This represents a potential new source of genetic markers of cancer and a new frontier for gene analysis of kidney and bladder cancers.

Bhalla and colleagues presented data that suggest nephron-sparing surgery is underutilized, as surgeons are opting to perform a laparoscopic radical nephrectomy rather than renal preservation.

Minimally Invasive Therapies for Kidney Cancer

Partial nephrectomy is currently considered the standard of care for small renal lesions at most centers of excellence. Bhalla and colleagues[156] presented data that suggest nephron-sparing surgery (NSS) is underutilized, as surgeons are opting to perform a laparoscopic radical nephrectomy rather than renal preservation. In their series of 158 patients with renal lesions of less than 4 cm, there was a significant decrease in postoperative creatinine clearance in patients treated with radical nephrectomy compared with those that received a partial nephrectomy ($P < .001$). Laparoscopic partial nephrectomy (LPN) allows for renal parenchymal preservation, using a minimally invasive technique. Spaliviero and colleagues[157] reported their experience with LPN in 300 consecutive patients. The authors noted that, with increasing experience, LPN is applicable to small tumors in difficult locations. In the last group of 100 patients, the increasing operative complexity resulted in slightly increased operative time (3.5 hours vs 3 hours; $P < .001$) and hospital stay (2.8 days vs 2 days; $P < .001$), but retained excellent cancer control and low complication rates.

Weld and coworkers[158] examined the role of tumor location in their experience with LPN in 121 patients. They reported an increase in collecting system violation, estimated blood loss, operative time, and overall complication rate as tumors progressed from exophytic to mesophytic to endophytic locations. Nadu and associates[159] examined the role of renal artery occlusion during LPN. These authors reported that arterial clamping with limited warm ischemia time resulted in lower mean blood loss (320 mL vs 510 mL; $P < .001$), and this did not negatively affect renal function as ascertained by DMSA scans obtained 3 months after the surgery.

Johnston and colleagues[160] reported their experience with 100 consecutive LPNs, comparing the use of fibrin-glue products and surgical bolsters. The authors reported that these sealants provided adequate hemostasis when compared with traditional suturing techniques, and there was no increase in postoperative hemorrhage. However, the authors cautioned that these products did not prevent significant complication rates in cases where the renal sinus or collecting system was entered.

Minimally invasive thermal ablative techniques were also well represented at this year's meeting. Gupta and colleagues[161] reported their experience with percutaneous renal cryoablation under CT guidance. Only 1 of 16 lesions demonstrated enhancement on follow-up surveillance CT imaging. Several groups have been exploring the use of this technology in more complex lesions. Warlick and associates[162] presented their experience with 8 patients with tumors abutting or adjacent to the collecting system at the time of CT-guided percutaneous cryoablation. None of these patients were found to have an adverse outcome such as fistula or obstruction postoperatively, which may represent an advantage over radiofrequency ablation (RFA) for the treatment of central tumors. Davol and coworkers[163] compared transperitoneal and retroperitoneal approaches for laparoscopic-assisted renal cryoablation. The authors reported that the transperitoneal approach was best suited for larger lesions in the upper pole in the anterior kidney, while the retroperitoneal approach was best suited for posterior lesions in patients with prior abdominal operations.

Milner and associates[164] reported the use of percutaneous CT-guided saline injection to mobilize bowel away

during renal cryoablation and thus avoid a bowel injury complication. Hayek and colleagues[165] reported their experience applying renal cryoablation to angiomyolipoma (AML). The procedure was performed in 5 patients without difficulty. Renal function was stable for all patients, and only 1 patient with giant bilateral AMLs had moderate bleeding requiring a blood transfusion. At 6 months follow-up, 3 patients with small lesions were free of disease, and 1 patient with a giant AML had > 50% reduction in tumor size; the last patient had not completed the 6-month follow-up. Shingleton and associates[166] reported their experience with using 3-D digital ultrasound to target cryoprobes for image-guided percutaneous cryoablation in a porcine model. This additional imaging technique allowed for visual confirmation that the lesion was completely involved within the iceball and confirmation of its relationship to adjacent organs.

Kidney Cancer: Staging and Surveillance

Cindolo and colleagues[167] compared the performance of 4 existing RCC staging nomograms for 2404 patients with localized RCC from 6 European centers. The Kattan nomogram and the UCLA integrated staging system (UISS) were found to be the 2 best performing models of overall survival, as well as DSS and RFS, defining the general applicability of prognostic models for predicting survival of patients with nonmetastatic RCC treated with nephrectomy.

Murphy and associates[168] reported the Columbia University experience with T3a tumors and concluded that absolute tumor size was significantly more important that capsular invasion, after evaluating 131 patients with T1N0M0, 19 patients with T2N0M0, and 82 patients with T3aN0M0 clear cell RCC. They found that patients with T3a disease had excellent 5-year survival rates (90.6%) that did not statistically differ from patients with T1 or T2 disease (92.2%; $P = .45$). Lam and associates[169] analyzed the prognostic significance of adrenal involvement in patients with T3 RCC in a large multicenter database of 5729 patients. Median survival for patients with T3 direct adrenal invasion was 14 months, compared with 70 months for patients with T3a perinephric or renal sinus fat involvement only, 50 months for patients with T3b without adrenal involvement, 21 months for patients with T3c without adrenal involvement, and 11 months for patients with T4 without adrenal involvement. The survival of patients with adrenal involvement more closely resembled that of patients with stage pT3c and pT4. Based on these data, consideration should be given to reclassifying tumors with adrenal invasion as a separate subcategory.

Two groups highlighted the importance of tumor necrosis as a prognostic factor in RCC. Lam and colleagues[170] reviewed 310 RCC specimens and found that the presence of histologic necrosis was associated with higher T stage, presence of metastases, higher tumor grade, greater mean tumor size, and greater Ki67 expression ($P < .001$). The extent of necrosis in the primary tumor also correlated with clinical factors as well as higher UISS risk category. Patients with necrosis had a lower 5-year DSS than patients without (36% vs 75%; $P < .001$). Further analysis demonstrated that the presence of necrosis was an independent predictor of survival for patients with localized disease, but not for those with metastatic disease.

Sengupta and coworkers[171] presented the Mayo Clinic experience with histologic coagulative necrosis in 3009 patients. The incidence of necrosis by histology was 28%, 46%, and 19% in clear cell, papillary, and chromophobe RCCs, respectively. Histologic coagulative tumor necrosis was associated with anemia, elevated erythrocyte sedimentation rate, large tumors (> 10 cm), and distant metastases. Necrosis was also associated with poorer survival for clear cell RCC patients in both univariate and multivariate analyses. Frank and colleagues[172] presented a protocol to tailor surveillance for RCC based on the tumor histology. Positive surgical margins, 2002 TNM stage, tumor size, Fuhrman grade, and tumor necrosis were reported to be independent predictors of abdominal recurrence in patients with clear cell RCC, and these same features, except surgical margins, were significantly associated with thoracic recurrence. For papillary RCC, 2002 TNM stage and tumor grade were independent predictors of thoracic and abdominal recurrence. No multivariate analysis was performed for chromophobe RCC due to the small number of abdominal and thoracic recurrences. However, recurrences in this group exhibited a clear stage- and grade-specific pattern.

Patients with RCC with necrosis had a lower 5-year DSS than patients without (36% vs 75%; P < .001). Further analysis demonstrated that the presence of necrosis was an independent predictor of survival for patients with localized disease, but not for those with metastatic disease.

Urothelial Carcinoma: Upper Urinary Tract

Several reports focused on the biology of upper tract TCC. Secin and

colleagues[173] evaluated the role of lymphadenectomy in 120 patients undergoing nephroureterectomy. Lymph node metastases were noted in 24 (20%) patients. The average number of resected lymph nodes was 5.1 (range 1-17) for a right-sided dissection and 9.1 (range 1-41) for a left-sided dissection. Patients with lymph node involvement were found to have a higher risk of disease recurrence and worse survival, with a cumulative 5-year probability of developing metastasis and/or dying of disease for N0 and N1-2 patients of 46.8% and 85.5%, respectively. Presence of suspicious lymph nodes on CT scan was the only preoperative variable predicting lymph node involvement.

Brausi and colleagues[174] also presented data supporting the role of lymph node dissection at the time of nephroureterectomy. The authors reviewed 82 patients with muscle-invasive TCC of the upper urinary tract and found a 29% incidence of lymph node involvement. Retroperitoneal lymph node dissection resulted in a significant improvement in time to disease recurrence, and was also found to be an independent predictor of survival in multivariate models.

These reports underscore the importance of lymph node dissection with nephroureterectomy for improved disease staging and treatment of muscle-invasive TCC of the upper urinary tract. ■

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